

Celsa 08/616,371

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(FILE 'HCAPLUS' ENTERED AT 11:27:47 ON 24 JUN 1997)

DEL HIS Y  
ACT CELSA/A

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L1 ( 11)SEA FILE=HCAPLUS ABB=ON NITROSOHB/OBI OR NITROSOHEMOGLOB  
L2 ( 209)SEA FILE=HCAPLUS ABB=ON (NITROSO/OBI OR NITROSYL/OBI) (L  
L3 ( 119)SEA FILE=HCAPLUS ABB=ON NITROSYLHEMOGLOBIN/OBI OR NITROS  
L4 249 SEA FILE=HCAPLUS ABB=ON L3 OR L2 OR L1

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ACT CELSA616/A

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L5 158 SEA FILE=HCAPLUS ABB=ON "STAMLER J"/AU OR "STAMLER J S"/

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~~L6~~ 4 S L5 AND L4 *see separate printout for inventor search*  
L7 6 S L4 (L) (PREPN OR PREPAR? OR MANUFAC? OR PRODN OR PRODUC  
L8 15956 S NITROSO OR NITROSYL  
L9 228 S L8 (L) THIOL# OR NITROSOTHIOL# OR NITROSYLTHIOL#  
L10 8 S L4 AND L9  
L11 5 S L4 (L) (DISEASE# OR DISORDER#)

FILE 'REGISTRY' ENTERED AT 11:58:07 ON 24 JUN 1997

E NITROGEN OXIDE/CN

L12 1 S E3

FILE 'HCAPLUS' ENTERED AT 11:58:23 ON 24 JUN 1997

L13 42251 S L12 OR NITROGEN OXIDE#  
~~L14 0 S L13 AND L14~~  
L15 16 S L13 AND L4  
L16 81869 S BLOOD PRESSURE OR SICKLE CELL OR INFLAMMA? OR ATHEROSCL  
L17 3 S L4 AND L16  
L18 1 S L4 AND FREE RADICAL  
L19 1 S L4 AND FREE RADICAL#  
L20 18 S L7 OR L10 OR L11 OR L17 OR L18 OR L19  
L21 14 S L15 NOT L20  
L22 0 S L21 AND (RELEAS? OR SCAVANG?)

=> d .ca 120 1-18

L20 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1997:310017 HCAPLUS

DN 126:274520

TI Method for measuring **nitrosyl [Fe(II)]-hemoglobin**  
in health and **disease**

IN Stamler, Jonathan S.

PA Duke University Medical Center, USA; Stamler, Jonathan S.

SO PCT Int. Appl., 18 pp.

CODEN: PIXXD2

PI WO 9710493 A1 970320

DS TT, W UA, W UG, W US, W UZ, W VN, W AM, W AZ, W BY, W KG, W KZ, W  
MD, W RU, W TJ, W TM, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ,  
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,  
PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,  
VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, BF, BJ, CF, CG, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT,  
LU, MC, NL, PT, SE

AI WO 96-US14660 960913  
 PRAI US 95-3801 950915  
 US 96-616259 960315  
 DT Patent  
 LA English  
 AB Nitrosyl [Fe(II)]-Hb can be detected in biol. samples, e.g., blood, by using a method that involves injection of samples into a photolysis cell, prior to detection of chemiluminescence generated by the reaction between nitric oxide and ozone. This method is useful for monitoring the levels of nitric oxide bioactivity in both normal physiol. states and disease states, such as septic shock, atherosclerosis, thrombosis, hyperhomocysteinemia, pulmonary hypertension, malignancy, infections, and central nervous system disorders.  
 IC ICM G01N021-63  
 ICS G01N021-76; G01N033-68  
 CC 9-5 (Biochemical Methods)  
 Section cross-reference(s): 3, 13, 14  
 ST blood **nitrosylHb** detn photolysis chemiluminescence  
**disease; nitroso thiol** detn photolysis  
 chemiluminescence  
 IT Serum albumin  
 RL: ANT (Analyte); ANST (Analytical study)  
 (S-**nitroso**; **nitrosyl** [Fe(II)]-**Hb**  
 detn. by photolysis/chemiluminescence in relation to nitric oxide  
 metab.)  
 IT **Hemoglobins**  
**Thiols** (organic), analysis  
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);  
 BIOL (Biological study); USES (Uses)  
 (S-**nitroso**; **nitrosyl** [Fe(II)]-**Hb**  
 detn. by photolysis/chemiluminescence in relation to nitric oxide  
 metab.)  
 IT Emission spectrometers  
 (chemiluminescence; **nitrosyl** [Fe(II)]-**Hb**  
 detn. by photolysis/chemiluminescence in relation to nitric oxide  
 metab.)  
 IT **Atherosclerosis**  
 Blood analysis  
 Central nervous system **diseases**  
**Diseases** (animal)  
 Erythrocyte  
 Infection  
 Photolysis  
 Pulmonary hypertension  
 Septic shock  
 Thrombosis  
 Tumors (animal)  
 (**nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)  
 IT **Hemoglobins**  
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);  
 BIOL (Biological study); USES (Uses)  
 (nitrosylHbs; **nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)  
 IT Proteins (specific proteins and subclasses)  
 RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);

BIOL (Biological study); USES (Uses)  
 (sulfoproteins, S-nitroso; **nitrosyl** [Fe(II)]-  
**Hb** detn. by photolysis/chemiluminescence in relation to  
 nitric oxide metab.)

IT 6027-13-0, Homocysteine  
 RL: ARG (Analytical reagent use); RCT (Reactant); ANST (Analytical  
 study); USES (Uses)  
 (metabolic disorders, hyperhomocysteinemia;  
**nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)

IT 51209-75-7, S-Nitroso-L-cysteine 56577-02-7, S-  
 Nitroso-N-acetyl-L-cysteine 57564-91-7,  
 S-Nitrosoglutathione  
 RL: ANT (Analyte); ANST (Analytical study)  
 (**nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)

IT 10102-43-9, Nitric oxide, analysis  
 RL: ANT (Analyte); BPR (Biological process); MFM (Metabolic  
 formation); RCT (Reactant); ANST (Analytical study); BIOL  
 (Biological study); FORM (Formation, nonpreparative); PROC (Process)  
 (**nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)

IT 10028-15-6, Ozone, reactions  
 RL: ARG (Analytical reagent use); RCT (Reactant); ANST (Analytical  
 study); USES (Uses)  
 (**nitrosyl** [Fe(II)]-**Hb** detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)

L20 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
 AN 1997:50797 HCAPLUS  
 DN 126:155746  
 TI Dynamic aspects of nitric oxide metabolism in health and disease  
 AU Minamiyama, Yukiko; Inoue, Masayasu  
 CS Med. Sch., Osaka City Univ., Osaka, 545, Japan  
 SO Kikan Kagaku Sosetsu (1996), 30, 143-150  
 CODEN: KKSOEC  
 DT Journal; General Review  
 LA Japanese  
 AB A review with 22 refs. Nitric oxide (NO) has been implicated to  
 play crit. roles in various physiol. processes including the  
 regulation of vascular resistance, platelet aggregation,  
 neurotransmission and immune reaction. However, details of the  
 dynamic aspects of NO metab. remain to be elucidated. The present  
 paper reports the metabolic fate of NO in the circulation and around  
 vascular walls in health and pathol. subjects. To elucidate the  
 fate of NO in the circulation, its adduct, were generated in RBC by  
 NaNO<sub>2</sub> and NOC7, NO donors, and the change in cellular levels of NO,  
 NO-Hb adducts (NO-Hb) and nitrite + nitrate in plasma and tissues  
 were detd. Based on the expts. using ESR (ESR) spectrometer,  
 kinetic aspects of the formation and degrdn. of NO-Hb and its  
 metabolites were described. Significant amts. of NO-Hb were  
 generated by incubating RBC with either NaNO<sub>2</sub> or NOC7. When  
 injected i.v. to normal rats, NO-Hb in NaNO<sub>2</sub> and NOC7-treated RBC  
 disappeared from the circulation RBC with a half-life of 30 and 16  
 min, resp. I.v. administration of either NaNO<sub>2</sub> or NOC7 increased  
 the blood levels of NO-Hb. The metabolic fate of NO-Hb differ  
 significantly with NaNO<sub>2</sub>- and NOC7-treated groups both in vivo and

in vitro. NO-Hb levels in NOC7-injected rats were significantly lower with animals administered GSH than with control group. These results suggested that the metabolic fate of NO might be affected by the thiol status of animals.

CC 14-0 (Mammalian Pathological Biochemistry)  
Section cross-reference(s): 2

IT **Hemoglobins**

RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)  
(**nitrosyl-**; nitric oxide metab. in health and disease)

L20 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1996:761663 HCAPLUS

DN 126:37023

TI Nitrosylated heme proteins as blood substitutes

IN Stamler, Jonathan

PA Brigham and Women's Hospital, USA

SO PCT Int. Appl., 130 pp.

CODEN: PIXXD2

PI WO 9630006 A1 961003

DS W: AU, CA, JP

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

AI WO 96-US3866 960325

PRAI US 95-409720 950324

DT Patent

LA English

AB Blood substitutes comprises a heme protein to which NO or NO<sub>2</sub> group is linked directly or indirectly. Tissue plasminogen activator (t-PA) was S-nitrosylated (prepn. given) and thrombolytic, anti-platelet, and vasodilator effects of S-NO-t-PA were studied.

IC ICM A61K031-14

ICS A61K031-715; A61K031-765; A61K038-16; C07D307-82

CC 63-3 (Pharmaceuticals)

Section cross-reference(s): 34

IT **Thiols**, biological studies

RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(S-**nitroso**; compns. contg. nitrosylated heme proteins as blood substitutes)

IT **Hemoglobins**

RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(**nitrosyl-**; compns. contg. nitrosylated heme proteins as blood substitutes)

L20 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1996:324363 HCAPLUS

DN 125:54447

TI Role of **thiols** in and around circulating erythrocytes in the metabolism of **nitrosyl-hemoglobin**

AU Minamiyama, Y.; Takemura, S.; Inoue, M.

CS Medical School, Osaka City University, Osaka, 545, Japan

SO Portland Press Proc. (1996), 10(Biology of Nitric Oxide Part 5), 123

CODEN: POPPEF

DT Journal  
 LA English  
 AB The thiol status in and around erythrocyte, including Cys34 of albumin appeared to play important role in the formation and degrdn. of nitrosyl-Hb (NO-Hb). In addn., NO and/or its metabolites also reacted with various thiols in vivo thereby forming stable S-nitrosothiols which may release bioactive NO depending of the redox state of animals.  
 CC 13-5 (Mammalian Biochemistry)  
 ST **thiol** erythrocyte **nitrosyl Hb** metab  
 IT Erythrocyte  
     (role of **thiols** in and around circulating erythrocytes in the metab. of **nitrosyl-Hb**)  
 IT **Thiols**, biological studies  
 RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)  
     (role of **thiols** in and around circulating erythrocytes in the metab. of **nitrosyl-Hb**)  
 IT **Hemoglobins**  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
     (**nitrosyl-**, role of **thiols** in and around circulating erythrocytes in the metab. of **nitrosyl-Hb**)  
 IT 10102-43-9, Nitric oxide, biological studies  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
     (role of **thiols** in and around circulating erythrocytes in the metab. of **nitrosyl-Hb**)

L20 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
 AN 1996:324257 HCAPLUS  
 DN 125:54485  
 TI **S-Nitrosohemoglobin: A new activity of blood involved in regulation of blood pressure**  
 AU Jia, Lee; Bonaventura, Celia; Bonaventura, Joseph; Stamler, Jonathan S.  
 CS Medical Center, Duke University, Durham, NC, 27710, USA  
 SO Portland Press Proc. (1996), 10(Biology of Nitric Oxide Part 5), 14  
 CODEN: POPPEF

DT Journal  
 LA English  
 AB New allosteric and/or electronic properties of Hb involved in regulation of vasomotor tone argue against the importance of free NO in transduction of such NO related activity, and suggest that S-NitrosoHbs could be used to overcome the hypertensive side effects of Hb-based blood substitutes.  
 CC 13-6 (Mammalian Biochemistry)  
 ST **nitrosoHb** NO blood pressure  
 IT **Blood pressure**  
     (**S-NitrosoHb** in regulation of **blood pressure**)  
 IT **Hemoglobins**  
 RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
     (**nitrosyl-**, **S-NitrosoHb** in regulation of

**blood pressure)**  
IT 10102-43-9, Nitric oxide, biological studies  
RL: BAC (Biological activity or effector, except adverse); BIOL  
(Biological study)  
(S-NitrosoHb in regulation of **blood  
pressure)**

L20 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1996:182211 HCAPLUS  
DN 124:298544  
TI S-Nitrosohemoglobin: a dynamic activity of blood involved  
in vascular control  
AU Jia, Li; Bonaventura, Celia; Bonaventura, Joseph; Stamler, Jonathan  
S.  
CS Dep. Med., Duke Univ. Med. Cent., Durham, NC, 27710, USA  
SO Nature (London) (1996), 380(6571), 221-6  
CODEN: NATUAS; ISSN: 0028-0836  
DT Journal  
LA English  
AB A dynamic cycle exists in which Hb is S-nitrosylated in the lung  
when red blood cells are oxygenated, and the NO group is released  
during arterial-venous transit. The vasoactivity of S-nitrosoHb is  
promoted by the erythrocytic export of S-nitrosothiols. These  
findings highlight newly discovered allosteric and electronic  
properties of Hb that appear to be involved in the control of blood  
pressure and which may facilitate efficient delivery of oxygen of  
tissues. The role of S-nitrosoHb in the transduction of NO-related  
activities may have therapeutic applications.

CC 63-3 (Pharmaceuticals)  
Section cross-reference(s): 13

ST **nitrosoHb nitrosothiol** NO blood vascular control  
IT Animal respiration  
Blood substitutes and Plasma expanders  
Blood vessel  
Erythrocyte  
Lung  
Signal transduction, biological  
(S-nitrosoHb in dynamic activity of blood involved in  
vascular control)

IT **Thiols**, biological studies  
RL: BPR (Biological process); MFM (Metabolic formation); BIOL  
(Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(S-nitroso, S-nitrosoHb in dynamic activity  
of blood involved in vascular control)

IT **Hemoglobins**  
RL: BPR (Biological process); MFM (Metabolic formation); BIOL  
(Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(**nitrosyl-**, S-nitrosoHb in dynamic activity  
of blood involved in vascular control)

IT 10102-43-9, Nitrogen oxide (NO), biological studies  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(S-nitrosoHb in dynamic activity of blood involved in  
vascular control)

L20 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1996:124340 HCAPLUS

DN 124:167965  
 TI Temporal relationships between levels of circulating NO derivatives, vascular NO production and hyporeactivity to noradrenaline induced by endotoxin in rats  
 AU Paya, Dominique; Maupoil, Veronique; Schott, Christa; Rochette, Luc; Stoclet, Jean-Claude  
 CS Laboratoire de Pharmacologie Cellulaire et Moleculaire, ULP, Illkirch, 67041, Fr.  
 SO Cardiovasc. Res. (1995), 30(6), 952-9  
 CODEN: CVREAU; ISSN: 0008-6363  
 DT Journal  
 LA English  
 AB Lipopolysaccharide (LPS) induces early (within 1 h) and delayed (after several hours) impairment of vascular reactivity to catecholamines whose mechanisms are different, although they probably both involve nitric oxide (NO). Temporal and quant. relationships between hyporeactivity to noradrenaline and NO prodn. were investigated in a rat model of endotoxemia allowing to clearly distinguish the two phases of hyporeactivity. Anesthetized rats were infused with LPS (14 mg kg<sup>-1</sup> h<sup>-1</sup>) for 1 h. Pressure responses to noradrenaline (NA) and circulating NO derivs. (nitrosyl Hb, NO-2, NO-3) were monitored for 5 h after the onset of infusion. Reactivity to NA and tissue cGMP level were also assessed ex vivo, in aortic rings taken at different exptl. times. LPS-induced early hyporeactivity to NA was assocd. with a moderate but significant increase in plasma NO-3 level, without any significant change in concn. of the other circulating NO derivs. Neither reactivity ex vivo nor cGMP content were modified in aortas taken after 1 h of LPS infusion. By contrast, delayed hyporeactivity (5 h after the onset of LPS infusion) was assocd. with a large increase in all circulating NO derivs. (up to 2.5 fold), enhanced aortic cGMP level and aortic hyporeactivity ex vivo. Pre-treatment of rats with NG-nitro-L-arginine Me ester (1 mg kg<sup>-1</sup> i.v.) entirely prevented early hyporeactivity and rise in NO-3 concn. In addn. it attenuated in comparable proportion both delayed hyporeactivity to NA in vivo and circulating levels of NO derivs. The results confirm the involvement of NO in the two phases of hyporeactivity to NA induced by LPS. They strongly support the view that a circulating factor is involved in triggering endothelial NO release during the early phase, whereas the delayed phase is assocd. with a high prodn. of NO in vascular smooth muscle resulting from the induction of NO synthase.  
 CC 4-5 (Toxicology)  
 IT **Hemoglobins**  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
 (nitrosyl-, circulating NO derivs., vascular NO prodn. and hyporeactivity to noradrenaline induced by endotoxin)  
 L20 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
 AN 1995:720167 HCAPLUS  
 DN 123:139881  
 TI **S-Nitrosothiols** and dinitrosyl iron complexes as source of nitric oxide in animals  
 AU Khrapova, N. V.; Melenkova, I. V.; Vanin, A. F.  
 CS N.N. Semenov Inst. Chem. Physics, Moscow, Russia

SO Biofizika (1995), 40(1), 117-21  
 CODEN: BIOFAI; ISSN: 0006-3029  
 DT Journal  
 LA Russian  
 AB It was established, by using EPR, that S-nitrosocysteine or S-nitrosohomocysteine become rapid degraded resulting in the release of nitric oxide (NO) and the formation of paramagnetic Hb nitrosyl complexes (Hb-NO) in murine blood. In the presence of exogenous iron in blood dinitrosyl non-heme iron complexes (DNIC) with thiol-contg. ligands, i.e. 2.03 complexes, were formed. Significant amts. of these complexes were formed, if low-mol.-wt. DNIC with cysteine or homocysteine was introduced to animals at iron/thiol ratios in complexes and soln. of 1:20 or 1:2. The 2.03 complexes were stable in the organism. Thus, the system of DNIC .dblharw. S-nitrosothiols predominates in the S-nitrosothiol conversion into DNIC.  
 CC 13-2 (Mammalian Biochemistry)  
 ST nitric oxide **nitrosothiol**; nitrosyl nonheme iron complex  
 nitric oxide  
 IT Blood  
 (nitrosothiols and dinitrosyl iron complexes as source of nitric oxide in animals)  
 IT **Hemoglobins**  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
 (nitrosyl complexes; **nitrosothiols** and dinitrosyl iron complexes as source of nitric oxide in animals)  
 IT **Thiols**, biological studies  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
 (nitroso, **nitrosothiols** and dinitrosyl iron complexes as source of nitric oxide in animals)  
 IT 7439-89-6D, Iron, dinitrosyl complexes 51209-75-7, S-Nitrosocysteine 139427-42-2, S-Nitrosohomocysteine  
 RL: BPR (Biological process); BIOL (Biological study); PROC (Process)  
 (nitrosothiols and dinitrosyl iron complexes as source of nitric oxide in animals)  
 IT 10102-43-9, Nitric oxide, biological studies  
 RL: MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)  
 (nitrosothiols and dinitrosyl iron complexes as source of nitric oxide in animals)

L20 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
 AN 1995:568714 HCAPLUS  
 DN 122:287483  
 TI Role of **thiols** in the targeting of S-nitroso **thiols** to red blood cells  
 AU Pietraforte, Donatella; Mallozzi, Cinzia; Scorza, Giuseppe; Minetti, Maurizio  
 CS Laboratorio di Biologia Cellulare, Istituto Superiore di Sanita, Rome, 00161, Italy  
 SO Biochemistry (1995), 34(21), 7177-85  
 CODEN: BICHAW; ISSN: 0006-2960  
 DT Journal  
 LA English



OS CJACS

AB The authors compared the .bul.NO-releasing characteristics of two NO donors, the S-nitroso adduct of bovine serum albumin (BSANO) and the S-nitroso adduct of L-glutathione (GSNO). In oxygenated phosphate buffer (pH 7.4) and in Hb soln., both NO donors released .bul.NO only in the presence of a low mol. wt. thiol (the most active was L-cysteine). The requirement of thiol to release .bul.NO strongly suggests that a transnitrosation reaction occurs between the S-nitroso adduct of the NO donor and the sulfhydryl group of the NO acceptor. The reaction produced a labile S-nitroso-L-cysteine intermediate that released .bul.NO. As shown by spin-trapping expts., the transnitrosation reaction involved the formation of .bul.NO (trapped by 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide) and .bul.S radicals (trapped by 5,5'-dimethyl-1-pyrroline N-oxide) of both the NO donors and the NO acceptor (L-cysteine). The reaction leading to .bul.S radical formation was distinct from the transnitrosation reaction, since it was oxygen-dependent. The authors suggest that .bul.S radicals are formed from oxidizing species produced after a reaction between .bul.NO and mol. oxygen (.bul.NO2 is a likely candidate). As for pure .bul.NO gas, the major oxidn. product of NO donors, in phosphate buffer (pH 7.4), was NO2-, with no formation of NO3-. In the presence of oxyHb, both NO donors produced only NO3-. BSANO and GSNO showed distinct patterns of .bul.NO release both in phosphate buffer and in the presence of Hb. In contrast to BSANO, GSNO oxidized HbO2 in intact cells at a much slower kinetic rate than with cell lysate or purified Hb. The fast kinetics of BSANO with intact cells suggests binding to the cell surface, where L-cysteine can allow the transport of .bul.NO to the cytoplasm. On account of their ability to oxidize .bul.NO to NO3-, red blood cells probably represent the last step in .bul.NO biotransformation or inactivation. The methHb formed in this process was reduced by the NADH-dependent methHb reductase pathway. The data suggest that sulfhydryl groups, and esp. L-cysteine, play a regulatory role in .bul.NO targeting to the red blood cells in plasma, thus buffering the concn. of .bul.NO. Moreover, the S-nitroso thiol group of serum albumin may intermediate between cells in the metab. or bioactivity of .bul.NO.

CC 13-5 (Mammalian Biochemistry)

ST **thiol targeting S nitroso thiol**  
erythrocyte

IT Mercapto group  
(**thiols** in targeting of S-nitroso  
**thiols** to erythrocytes)

IT **Hemoglobins, oxy-**  
RL: BAC (Biological activity or effector, except adverse); BIOL  
(Biological study)  
(**thiols** in targeting of S-nitroso  
**thiols** to erythrocytes)

IT **Albumins, biological studies**  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(S-nitroso, **thiols** in targeting of S-  
**nitroso thiols** to erythrocytes)

IT **Nitrosation**  
(trans-, **thiols** in targeting of S-nitroso  
**thiols** to erythrocytes)

IT 52-90-4, L-Cysteine, biological studies 57564-91-7,  
s-Nitrosoglutathione  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(thiols in targeting of S-nitroso  
thiols to erythrocytes)

IT 14797-55-8, Nitrate, biological studies  
RL: MFM (Metabolic formation); BIOL (Biological study); FORM  
(Formation, nonpreparative)  
(thiols in targeting of S-nitroso  
thiols to erythrocytes)

L20 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1995:349193 HCAPLUS  
DN 122:130100  
TI Targets of nitric oxide in a mouse model of liver  
inflammation by Corynebacterium parvum

AU Chamulitrat, Walee; Jordan, Sandra J.; Mason, Ronald P.; Litton, Amy  
L.; Wilson, Joan G.; Wood, Edgar R.; Wolberg, Gerald; Molina y  
Vedia, Luis

CS Laboratory Molecular Biophysics, National Institutes Health,  
Research Triangle Park, NC, 27709, USA

SO Arch. Biochem. Biophys. (1995), 316(1), 30-7  
CODEN: ABBIA4; ISSN: 0003-9861

DT Journal  
LA English

AB Treatment of mice with Corynebacterium parvum induces chronic  
inflammation. This treatment followed by an injection of  
lipopolysaccharide (LPS) produces hepatic necrosis and death. We  
examd. liver tissue by using ESR (EPR) spectroscopy and found that,  
in addn. to the previously reported nonheme nitrosyl complexes, heme  
nitrosyl complexes were also formed. Hb nitrosyl complexes measured  
in the whole blood of mice treated with C. parvum were not increased  
after addnl. LPS treatment. However, this treatment significantly  
increased the heme nitrosyl complexes in the liver, whereas the  
nonheme nitrosyl complex concn. was unaffected. EPR signals from  
whole blood and liver tissues from mice treated with C. parvum and  
C. parvum + LPS were inhibited by prolonged treatment with  
NG-monomethyl-L-arginine (L-NMA). Nitric oxide (.bul.NO) is known  
to bind to cytochrome P 450/P420 peaks in the livers of mice treated  
with C. parvum and C. parvum + LPS. By performing analyses of EPR  
spectra obtained from hepatocytes exposed to .bul.NO, we were able  
to unambiguously identify EPR signals attributable to cytochrome  
P420 and nonheme nitrosyl complexes in the livers of both  
treatments. Deconvolution of the composite in vivo EPR spectra  
indicated that Hb nitrosyl complexes contributed weakly in the C.  
parvum livers, but threefold more in the C. parvum + LPS livers,  
suggesting that hemorrhage may have occurred. Expts. with L-NMA  
treatment revealed that this addnl. .bul.NO prodn. did not correlate  
with hepatic necrosis and onset of death. Immunopptn. of liver  
cytosols from C. parvum- and (C. parvum + LPS)-treated mice using an  
antibody against mouse inducible nitric oxide synthase showed that  
this enzyme was indeed present in the cytosolic fractions and was  
absent in those from control livers. Our novel detection of  
cytochrome P420 nitrosyl complex in vivo may be linked to any role  
of hepatic P 450's functions during liver inflammation.

CC 14-7 (Mammalian Pathological Biochemistry)

ST **Hb nitrosyl complex liver inflammation**  
; cytochrome P420 **nitrosyl complex liver**  
**inflammation**; nitric oxide target liver **inflammation**

IT Corynebacterium parvum  
(**Hb nitrosyl complex formation in liver**  
during chronic and acute **inflammation** induced by  
Corynebacterium parvum)

IT Liver, **disease**  
(**inflammation, Hb nitrosyl complex**  
formation in liver during chronic and acute **inflammation**  
induced by Corynebacterium parvum)

IT **Hemoglobins**  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(**nitrosyl-, Hb nitrosyl complex**  
formation in liver during chronic and acute **inflammation**  
induced by Corynebacterium parvum)

IT Proteins, specific or class  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(nonheme iron-contg., nitrosyl complexes; formation in liver  
during chronic and acute **inflammation** induced by  
Corynebacterium parvum of)

IT 14452-93-8, **Nitrosyl**  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological  
study)  
(**Hb and nonheme protein complexes; formation in liver**  
during chronic and acute **inflammation** induced by  
Corynebacterium parvum of)

IT 9035-49-8D, Cytochrome P 420, **nitrosyl complexes**  
9035-51-2D, Cytochrome P 450, **nitrosyl complexes**  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)  
(**Hb nitrosyl complex formation in liver**  
during chronic and acute **inflammation** induced by  
Corynebacterium parvum)

IT 10102-43-9, Nitric oxide, biological studies  
RL: ADV (Adverse effect, including toxicity); BIOL (Biological  
study)  
(targets of nitric oxide in mouse model of liver  
**inflammation** by Corynebacterium parvum)

L20 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1994:602305 HCAPLUS  
DN 121:202305  
TI **Nitrosyl hemoglobin production during**  
reperfusion after focal cerebral ischemia in rats  
AU Kumura, Eiji; Yoshimine, Toshiki; Tanaka, Satonori; Hayakawa, Toru;  
Shiga, Takeshi; Kosaka, Hiroaki  
CS Physiology, Osaka, Japan  
SO Neurosci. Lett. (1994), 177(1-2), 165-7  
CODEN: NELED5; ISSN: 0304-3940  
DT Journal  
LA English  
AB The authors first detected a definite nitrosyl Hb (HbNO) signal in  
the jugular blood by ESR spectroscopy during early reperfusion after  
cerebral ischemia. A distinct three-line hyperfine structure,

characteristic to HbNO, was demonstrated at 30 min of recirculation after 2 h of middle cerebral artery occlusion in rats. Only a weak HbNO signal was obsd. in animals with 2 h sustained ischemia or with sham operation. The present findings suggest that reperfusion after cerebral ischemia facilitates nitric oxide generation in the brain, which leads to the increased nitrosylation of erythrocyte Hb in the cerebral circulating blood.

CC 14-10 (Mammalian Pathological Biochemistry)

IT Nitrosation

(**nitrosyl Hb prodn.** during  
reperfusion after focal cerebral ischemia in rats)

IT Brain, **disease**

(ischemia, focal, **nitrosyl Hb prodn.**  
. during reperfusion after focal cerebral ischemia in rats)

IT **Hemoglobins**

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)

(**nitrosyl-, nitrosyl Hb  
prodn.** during reperfusion after focal cerebral ischemia  
in rats)

IT Perfusion

(re-, **nitrosyl Hb prodn.** during  
reperfusion after focal cerebral ischemia in rats)

IT 10102-43-9, Nitric oxide, biological studies

RL: ADV (Adverse effect, including toxicity); BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)

(**nitrosyl Hb prodn.** during  
reperfusion after focal cerebral ischemia in rats)

L20 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1994:7135 HCAPLUS

DN 120:7135

TI Augmentation of cooked cured meat color by **nitrosohemoglobin  
prepared** from cattle blood

AU Sakata, Ryoichi; Yoshida, Naoko; Morita, Hidetoshi; Nagata, Yukiharu

CS Sch. Vet. Med., Azabu Univ., Sagami-hara, 229, Japan

SO Anim. Sci. Technol. (1993), 64(8), 855-61

CODEN: ALSTEQ

DT Journal

LA Japanese

AB The red cell fraction of animal blood is presently used only to a limited degree in food industries. For use of this fraction as a food component, nitrosation of Hb was examd. for coloration in meat processing and redn. of nitrite content in processed meat products. The purified Hb fraction (98.1%) was prepd. from cattle blood, and optimum reaction conditions for nitrosation of Hb were detd. The nitrosylHb was added to exptl. sausage and its capacity to enhance meat product color was assessed. More than 80% of the total Hb in a reaction mixt. (pH 4.5) of 25 mM NaNO<sub>2</sub>-25 mM ascorbic acid (AsA) was rapidly nitrosated at 2.degree. and 20.degree.. The presence of 40% glucose in the Hb reaction mixt. improved the stability of the nitrosylHb. Stability was maintained for as long as 20 days at 2.degree.. Added nitrite in a nitrosylHb mixt. virtually disappeared and no aerobic bacteria could be detected after 3 days of 2.degree. or 20.degree. storage with/without glucose. When 0.5% or 1% of the nitrosylHb reaction mixt. was added to porcine loin meat with non-meat protein ingredient soln. (NaCl, NaNO<sub>2</sub>, and

Na-AsA), nitrosoheme pigment formation was greater than that of the control (without addn. of nitrosylHb) meat product, and added nitrosylHb showed quant. effects the color formation in sausage. Hunter color values of the sausage remained essentially unchanged for 2 wk of storage at 2.degree.. The color stability of the nitrosylHb added sample appeared essentially the same as that of the control under fluorescent lighting, and red color was better retained. TBA values were quite low and showed only slight variation, indicating lipid oxidn. not to have occurred after 2 wk of storage when nitrosylHb prep. from cattle blood has been added to sausage.

CC 17-7 (Food and Feed Chemistry)

IT **Hemoglobins**

RL: SPN (Synthetic preparation); PREP (Preparation)  
(**nitrosyl-**, **prepn.** of and use as sausage  
colorant)

L20 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1990:3828 HCAPLUS

DN 112:3828

TI Direct ESR measurement of **free radicals** in mouse  
pancreatic lesions

AU Nonaka, Atsushi; Manabe, Tadao; Asano, Noboru; Kyogoku, Takahisa;  
Imanishi, Katsuhiko; Tamura, Kohichiro; Tobe, Takayoshi; Sugiura,  
Yukio; Makino, Keisuke

CS Fac. Med., Kyoto Univ., Kyoto, 606, Japan

SO Int. J. Pancreatol. (1989), 5(2), 203-11

CODEN: IJPNEX; ISSN: 0169-4197

DT Journal

LA English

AB In this expt., free radicals in the pancreas of endotoxemia and  
ethionine-induced acute pancreatitis in mice were detected directly  
by ESR spectroscopy, using 77 K freeze-trapping and 25.degree. DMPO  
spin trapping techniques. In the 77 K freeze-trapping method,  
Mn(II) ion and R00.bul. radical were detected in endotoxemia and  
ethionine-induced pancreatic lesions. The heme-.ovrhdot.NO radical  
was obsd. at 6 and 24 h after isolation of the normal pancreas, and  
signal intensity was increased with time. This finding supports  
that ESR spectroscopy is a useful method for detecting the tissue  
degeneration process from ischemia to necrosis. Using the DMPO spin  
trapping technique (25.degree.), 6-line was detected at 6 h after  
i.p. administration of Escherichia coli in the model of endotoxemia,  
and 3- and 6-lines and a signal suggestive of DMPO-OH adduct were  
noted at 12 and 24 h in ethionine pancreatitis. These findings  
suggest that impaired pancreatic tissues exist in a considerably  
oxidative environment and O-derived free radicals may play an  
important role in the development of pancreatic lesions.

CC 9-5 (Biochemical Methods)

Section cross-reference(s): 13, 14

ST pancreas **free radical** detection ESR  
spectrometry; pancreatitis **free radical**  
detection ESR spectrometry

IT Pancreas, composition

(**free radicals** in, ESR spectrometry detection  
of)

IT Spectrochemical analysis

(ESR, **free radicals** in pancreas detection by,

- pancreatic disease in relation to)
- IT Toxins  
(endo-, metabolic disorders, endotoxemia, pancreatic lesions induced by, **free radical** detection by ESR spectrometry in)
- IT **Hemoglobins**  
RL: ANT (Analyte); ANST (Analytical study)  
(**nitrosyl**-, detection of, in pancreas by ESR spectrometry, pancreatic **disorders** in relation to)
- IT Pancreas, disease or disorder  
(pancreatitis, **free radicals** in, ESR spectrometry detection of)
- L20 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1988:182434 HCAPLUS  
DN 108:182434  
TI Oxidation of the 2-hydroxyamino derivative of 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole (Glu-P-1) to its 2-**nitroso** form, an ultimate form reacting with **hemoglobin thiol** groups
- AU Umemoto, Atsushi; Monden, Yasumasa; Tsuda, Mitsuhito; Grivas, Spiros; Sugimura, Takashi  
CS Biochem. Div., Natl. Cancer Cent. Res. Inst., Tokyo, 104, Japan  
SO Biochem. Biophys. Res. Commun. (1988), 151(3), 1326-31  
CODEN: BBRCA9; ISSN: 0006-291X  
DT Journal  
LA English
- AB The binding to Hb of synthetic 2-hydroxyamino-6-methyldipyrido[1,2-a:3',2'-d]imidazole and its oxidn. product 2-nitroso-6-methyldipyrido[1,2-a:3',2'-d]imidazole from the carcinogenic product of L-glutamic acid pyrolysis 2-amino-6-methyldipyrido[1,2-a:3',2'-d]imidazole were investigated in vitro. The hydroxylamine required oxidn. to its nitroso deriv. to bind to rat Hb through SH groups. Oxidn. of the hydroxylamine to the nitroso form was found to be enhanced by oxyHb and superoxide dismutase at pH 7.4 under aerobic conditions. Since these conditions might also enhance the oxidn. in vivo, the conversion of the DNA-reactive arylhydroxylamine to the DNA-nonreactive nitroso compds. and their subsequent binding to highly abundant SH groups of proteins could be considered as a process for detoxification of toxic arylhydroxylamines.
- CC 6-3 (General Biochemistry)  
Section cross-reference(s): 4
- ST hydroxylamine deriv oxidn **Hb** binding sulfhydryl;  
**nitroso** hydroxylamine **Hb** binding sulfhydryl
- IT **Hemoglobins**, met-  
**Hemoglobins**, oxy-  
RL: BIOL (Biological study)  
(arylhydroxylamine and **nitroso** deriv. binding to)
- L20 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 1997 ACS  
AN 1985:94472 HCAPLUS  
DN 102:94472  
TI Nitrosylhemoglobin, a suitable dye for vegetable proteins texturized by extrusion cooking
- AU Noel, P.; Culioli, J.; Melcion, J. P.; Goutefongea, R.; Coquillet, R.  
CS Lab. Aliment. Origine Anim., INRA, Nantes, 44072, Fr.

SO Lebensm.-Wiss. Technol. (1984), 17(6), 305-10  
 CODEN: LBWTAP; ISSN: 0460-1173

DT Journal

LA French

AB In meat products, partial substitution of meat by vegetable proteins results in color fading. Addn. of nitrosylHb prevents this drawback and restores a meatlike color to the product. Nitrosation of Hb can take place either before or after the texturization. This treatment was applied to pea and soy protein concs. The color of the treated product was studied by means of reflectance spectrophotometry between 400 and 700 nm. Readings took place just after the processing and at day 3, 7, 15, and 21 of storage. The most attractive color was obtained when Hb was nitrosated before texturization. When samples were stored under vacuum in the dark, the color was stable throughout the storage period. Therefore, light may be considered the main deleterious factor for color. With Hb concns. ranging from 3 to 10%, the color of the resulting products can be readily adjusted on a frankfurter type sausage products. The level of residual nitrite is similar to that usually found in traditional cured meat products.

CC 17-6 (Food and Feed Chemistry)

IT Color  
 (of **nitrosylHb**-contg. extruded texturized proteins, for meat **products**)

IT Pea  
 Soybean  
 (protein of, **nitrosylHb** coloring material for extruded, for meat **products**)

IT Proteins  
 RL: BIOL (Biological study)  
 (texturized vegetable, **nitrosylHb** as coloring material for, in meat **products**)

IT **Hemoglobins**  
 RL: BIOL (Biological study)  
 (**nitrosyl**-, as coloring material, for extruded texturized vegetable proteins, in meat **products**)

L20 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1984:21772 HCAPLUS

DN 100:21772

TI Attempt to obtain a **preparation** of beef **nitrosohemoglobin**

AU Jankiewicz, Leonard; Wasilewski, Stanislaw; Skrzypczynska, Elzbieta

CS Zakl. Technol. Miesa, SGGW-AR, Warsaw, 03-849, Pol.

SO Przem. Spozyw. (1983), 37(1), 28-30  
 CODEN: PRSPAD; ISSN: 0033-250X

DT Journal

LA Polish

AB An attempt to obtain beef nitrosoHb prepn. (responsible for meat coloring during curing with nitrates) was made using nitrosation of Hb, HbO<sub>2</sub>, and methHb solns. with gaseous NO for 3.5-8 min. MethHb and HbO<sub>2</sub> reacted poorly with NO (0.4-13.1%). Hb reacted at 43.3% when the reaction time was .apprx.8 min. An increase in reaction time to 9 min resulted in reaction of .apprx.75% of theHb. Use of NaNO<sub>2</sub> for nitrosation of Hb solns. was not effective. However, combination of NaNO<sub>2</sub> (.gtoreq.0.418 g/100 g Hb) with ascorbic acid [50-81-7] (12%) led to nitrosation of .ltoreq.89% of the Hb. This prepn. gave the

bright red color characteristic for nitrosoHb.

CC 17-13 (Food and Feed Chemistry)

ST Hb nitrosation nitrite **nitrosoHb**; nitrogen oxide Hb nitrosation; meat colorant **prepn** Hb nitrosation

IT Meat  
(**nitrosoHb** colorant **prepn.** for, by Hb nitrosation)

IT **Hemoglobins**, met-  
RL: SPN (Synthetic preparation); PREP (Preparation)  
(**nitroso-**, **prepn.** of, by **Hb** nitrosation, for meat coloring)

IT 50-81-7, biological studies 7632-00-0 10102-43-9, biological studies  
RL: BIOL (Biological study)  
(in Hb nitrosation, for **nitrosoHb prepn.**, meat coloring in relation to)

L20 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1982:139192 HCAPLUS

DN 96:139192

TI Preparation of derivatives of ferrous and ferric hemoglobin

AU Di Iorio, Ernesto E.

CS Lab. Biochem., ETH-Zurich, Zurich, 8092, Switz.

SO Methods Enzymol. (1981), 76(Hemoglobins), 57-72  
CODEN: MENZAU; ISSN: 0076-6879

DT Journal

LA English

AB Preparative procedures for ferrous Hb derivs. are detailed for deoxyHb, oxyHb, NO Hb, carbonylHb, nitroso arom. Hb, and alkylisocyanide derivs. Ferric Hb deriv. prepn. procedures are described for cyanomethHb.

CC 9-10 (Biochemical Methods)

IT **Hemoglobins**  
RL: PREP (Preparation)  
(**nitrosyl-**, **prepn.** of)

L20 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 1997 ACS

AN 1976:29296 HCAPLUS

DN 84:29296

TI Stability of nitroso derivatives (**nitrosothiols**, nitrosophenols, and **nitrosohemoglobin**) at alkaline pH

AU Cantoni, Carlo; Bianchi, Maria A.; Beretta, Giuseppe

CS Ist. Ispezione Aliment. Origine Anim., Univ. Milano, Milan, Italy

SO Ind. Aliment. (Pinerolo, Italy) (1975), 14(7-8), 79-81  
CODEN: INALBB

DT Journal

LA Italian

AB Nitrosophenol [104-91-6] and nitrosohemoglobin were stable when exposed to alk. conditions (pH 7-9) in soln. for .ltoreq.48 hr, whereas nitrosocysteine [51209-75-7] and nitrosoglutathione [57564-91-7] were unstable, decomp. with the release of NO<sub>2</sub><sup>-</sup>. The nitrosophenol, nitrosocysteine, and nitrosoglutathione were prepd. by the reaction of PhOH [108-95-2], cysteine [52-90-4], and glutathione [70-18-8], resp., with NaNO<sub>2</sub> in ice-cold N HCl. The formation of such nitroso compds. from ingested NO<sub>2</sub><sup>-</sup> in the acid conditions of the stomach and their breakdown under the alk. conditions of the small intestine are discussed.



CC 17-2 (Foods)

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L1 QUE ABB=ON NITROSOHB/OBI OR NITROSOHEMOGLOBIN#/OBI OR S  
NOHB/OBI OR S NOHB/OBI  
L2 QUE ABB=ON (NITROSO/OBI OR NITROSYL/OBI) (L) (HB/OBI OR  
HEMOGLOBIN#/OBI)  
L3 QUE ABB=ON NITROSYLHEMOGLOBIN/OBI OR NITROSYLHB/OBI  
L4 QUE ABB=ON L3 OR L2 OR L1  
L5 3 SEA FILE=WPIDS ABB=ON NITROSOHB OR NITROSOHAEMOGLOBIN# O  
R NITROSYLHAEMOGLOBIN# OR SNOHB OR NOHB OR (NITROSYL OR N  
ITROSO ) (2W) (HAEMOGLOBIN# OR HEMOGLOBIN#)  
L6 7 SEA FILE=WPIDS ABB=ON NITROSYLHB OR L5 OR L4  
L7 3 SEA FILE=WPIDS ABB=ON NITROSYL? (2A) (HB OR HEMOGLOBIN#  
OR HAEMOGLOBIN#)  
L8 9 SEA FILE=WPIDS ABB=ON L7 OR L6

=> d .wp 1-8

L8 ANSWER 1 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 97-212535 [19] WPIDS

CR 97-202348 [18]; 97-212491 [18]

DNC C97-068560

TI Nitrosated or nitrated haemoglobin(s), their prepn. and uses - e.g.  
to oxygenate, to scavenge free radicals or release nitric oxide gps.  
to tissues and treat ischaemic injury, hypertension, angina.

DC B04 B05 D22

IN STAMLER, J S

PA (UYDU-N) UNIV DUKE MEDICAL CENT

CYC 74

PI WO 9710265 A1 970320 (9719)\* EN 83 pp

RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA  
PT SD SE SZ UG

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI  
GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA  
UG US UZ VN

ADT WO 9710265 A1 WO 96-US14659 960913

PRAI US 96-667003 960620; US 95-3801 950915; US 96-616371 960315

AB WO 9710265 A UPAB: 970512

Delivering nitro-oxide to in a mammal comprises administering a low  
molecular weight nitrosating agent to the mammal.

Also claimed are: (1) a method for preparing S-nitroso

-haemoglobin (SNO-Hb)(FeII) specifically

S-nitrosylated on thiol groups, by incubating excess nitrosating agent with purified Hb in the absence of O<sub>2</sub>;

(2) a method for preparing SNO-Hb(FeII) O<sub>2</sub>, specifically S-nitrosylated on thiol groups (without oxidation of heme Fe) by incubating excess nitrosating agent with purified Hb in the presence of O<sub>2</sub>;

(3) a method for regulating delivery of O<sub>2</sub> and NO, in various redox forms, by administering a mixture of a low molecular weight thiol or nitroso-thiol and Hb or nitrosated Hb;

(4) use of a blood substitute comprising nitrosated Hb for delivering NO, for scavenging oxygen free radicals and NO and reducing blood pressure;

(5) a blood substitute comprising nitrosated or nitrated Hb and its uses;

(6) a method for regulating platelet activation by admin. of a composition comprising a substance (II) which controls the allosteric equilibrium or spin state of Hb;

(7) methods for forming poly-nitrosated Hb and poly-nitrated Hb (see 'Preferred Method'), and

(8) a composition comprising poly-nitrosated Hb.

USE - The method is used to increase the O<sub>2</sub> delivery capacity of Hb in a mammal suffering from shock, angina, stroke, reperfusion injury, acute lung injury, sickle cell anaemia and infection of red blood cells.

S-nitroso-thiol (RSNO) can be used to treat a blood borne disease (e.g. malaria) by isolating red blood cells, treating them with RSNO and re-administering them to the patient.

Nitrosated or nitrated Hb can be used to treat heart, brain, vascular and lung diseases; atherosclerosis and inflammation; also diseases resulting from platelet activation or adherence (e.g. myocardial infarction, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, sepsis and unstable angina).

Nitrosated Hb can also be used to treat stroke, angina, respiratory distress syndrome, and diseases or conditions with abnormalities of NO and oxygen metabolism (e.g. heart and lung diseases, sickle-cell anaemia, stroke, sepsis and organ transplantation); and to prevent thrombus formation.

Nitrosated Hb is also used to keep organs alive ex vivo to use for transplantation (all claimed).  
Dwg.0/11

L8 ANSWER 2 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 97-202348 [18] WPIDS  
CR 97-212491 [18]; 97-212535 [18]  
DNN N97-167201 DNC C97-064778  
TI Method for measuring nitrosyl iron (II)  
haemoglobin in blood - or assaying nitric oxide prodn. in  
disease states, e.g. septic shock, cardiogenic shock,  
atherosclerosis, thrombosis and pulmonary hypertension.  
DC B04 S03  
IN STAMLER, J S  
PA (UYDU-N) UNIV DUKE MEDICAL CENT  
CYC 74  
PI WO 9710493 A1 970320 (9718)\* EN 19 pp  
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA

PT SD SE SZ UG

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI  
GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA  
UG US UZ VN

ADT WO 9710493 A1 WO 96-US14660 960913

PRAI US 96-616259 960315; US 95-3801 950915

AB WO 9710493 A UPAB: 970516

Method of measuring **nitrosyl Fe(II)-haemoglobin**

in blood or assaying nitric oxide prodn. in disease states  
comprises: (a) lysing the red blood cells of a blood sample; (b)  
prepg. a protein fraction of the lysed red blood cells; (c)  
subjecting a protein fraction to photolysis; and (d) quantitating  
the amt. of nitric oxide in the protein fraction by measuring a  
chemiluminescence signal generated by a chemical reaction between  
nitric oxide and ozone.

USE - Nitric oxide levels can be monitored in disease states,  
e.g. septic shock, cardiogenic shock, hypovolemic shock,  
atherosclerosis, hyperhomocysteinemia, venous thrombosis, arterial  
thrombosis, coronary occlusion, pulmonary embolism, cerebrovascular  
accidents, vascular fibrosis, ectopic lentis, osteoporosis, mental  
retardation, skeletal deformities, pulmonary hypertension,  
malignancy, infections, inflammation, asthma, tolerance to narcotics  
and central nervous system disorders.

ADVANTAGE - The method is more sensitive than previous methods  
using electron paramagnetic resonance.  
Dwg.0/0

L8 ANSWER 3 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 96-454984 [45] WPIDS

DNC C96-142594

TI Blood substitute compsns. used for e.g. treating cardiovascular  
disorders - comprising, e.g. haemoglobin which is directly or  
indirectly linked to a nitrosyl gp..

DC B04

IN STAMLER, J

PA (BGHM) BRIGHAM & WOMENS HOSPITAL

CYC 20

PI WO 9630006 A1 961003 (9645)\* EN 131 pp

RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: AU CA JP

AU 9653682 A 961016 (9706)

ADT WO 9630006 A1 WO 96-US3866 960325; AU 9653682 A AU 96-53682 960325

FDT AU 9653682 A Based on WO 9630006

PRAI US 95-409720 950324

AB WO 9630006 A UPAB: 961111

A cpd. comprising a blood substitute to which an NO or NO2 gp. is  
directly or indirectly linked. Also claimed is a blood substitute  
compsn. comprising the cpd. described above and a carrier.

The blood substitute is a haem protein, such as an opt.  
modified human or bovine haemoglobin. the cpd. is an S-nitroso,  
N-nitroso, O-nitroso or C-nitroso cpd. The blood substitute compsn.  
also comprises an additional component selected from phospholipids,  
nonionic surfactants, emulsifiers, and fatty acids.

USE - The nitrosylated blood substituents may be used for  
effecting vasodilation, platelet inhibition of thrombolysis, and for  
treating cardiovascular disorders. The blood substitute compsns. may

also be used to maintain and perfuse transplant organs during transport. Other nitrosylated cpds., such as S-nitroso-albumin, may be used for causing relaxation of airway smooth muscle and for treatment of e.g. respiratory disorders. Admin. of the cpds. is e.g. oral or parenteral.

**ADVANTAGE - Nitrosylation of haemoglobin**  
increases haemoglobin-oxygen binding and can thus lead to an increase in the oxygen-carrying capacity of the blood.  
Dwg.1/33

L8 ANSWER 4 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 94-332842 [41] WPIDS  
DNN N94-261274 DNC C94-151360  
TI Admin of e.g. nitric oxide by inhalation - is useful for treatment of pulmonary emboli, angina pectoris, acute respiratory distress syndrome, etc..  
DC B05 B06 B07 P34  
IN FROSTELL, C G; HEDENSTIERNA, G; HOGMAN, M E; LOSCALZO, J; STAMLER, J S; FROSTELL, C  
PA (BGHM) BRIGHAM & WOMENS HOSPITAL  
CYC 3  
PI WO 9422499 A1 941013 (9441)\* EN 28 pp  
AU 9464968 A 941024 (9505)  
US 5427797 A 950627 (9531) 7 pp  
EP 692984 A1 960124 (9609) EN  
JP 09500609 W 970121 (9713) 19 pp  
ADT WO 9422499 A1 WO 94-US3561 940331; AU 9464968 A AU 94-64968 940331; US 5427797 A US 93-43653 930406; EP 692984 A1 EP 94-912377 940331, WO 94-US3561 940331; JP 09500609 W JP 94-522387 940331, WO 94-US3561 940331  
FDT AU 9464968 A Based on WO 9422499; EP 692984 A1 Based on WO 9422499; JP 09500609 W Based on WO 9422499  
PRAI US 93-43653 930406  
AB WO 9422499 A UPAB: 941206

The following are claimed: (A) methods for (i) systemic prevention or treatment of systemic blood platelet aggregation and coagulation, (ii) prevention or treatment of acute coronary syndromes including angina pectoris or (iii) prevention or treatment of acute respiratory distress syndrome, comprising admin., by the inhalation route, of a cpd. selected from nitric oxide and cpds. that deliver nitric oxide upon admin..

Also claimed is prevention or treatment of pulmonary emboli comprising admin., to the lung, of a pharmaceutical compsn. comprising a cpd. selected from nitric oxide and cpds. which deliver nitric oxide upon admin..

Dosage is 1 pg-1 mg per kg of body wt.  
Dwg.0/1

L8 ~~ANSWER 5 OF 9~~ WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN ~~93-182246 [22]~~ WPIDS  
DNC C93-080681  
TI Proteins comprising nitrosylated sulphur-hydrogen gps. e.g. S-nitroso-T-PA - regulate protein and cellular functions, for treating and preventing emphysema, asthma, bronchitis, fibrosis etc..  
DC B04 D16  
IN LOSCALZO, J; SIMON, D; SINGEL, D; STAMLER, J

PA (BGHM) BRIGHAM & WOMENS HOSPITAL

CYC 2

PI WO 9309806 A1 930527 (9322)\* EN 114 pp

AU 9230715 A 930615 (9340)

EP 676964 A1 951018 (9546) EN

US 5593876 A 970114 (9709) 58 pp

ADT WO 9309806 A1 WO 92-US9667 921113; AU 9230715 A AU 92-30715 921113;  
EP 676964 A1 EP 92-924388 921113, WO 92-US9667 921113; US 5593876 A  
CIP of US 91-791668 911114, Div ex US 92-943835 920914, Div ex US  
94-198854 940217, US 94-287830 940809

FDT AU 9230715 A Based on WO 9309806; EP 676964 A1 Based on WO 9309806

PRAI US 92-943835 920914; US 91-791668 911114; US 94-198854 940217;  
US 94-287830 940809

AB WO 9309806 A UPAB: 931115

The following are claimed: (A) a cpd. comprising S-nitroso-enzyme;  
the enzyme may be e.g. tissue-type plasminogen activator (tPA),  
streptokinase, urokinase or cathepsin; (B) a cpd. comprising  
S-nitroso -lipoprotein; the lipoprotein may be e.g. chylomicrons,  
very low density lipoprotein or high-density lipoprotein; (C) a  
compsn. comprising S-nitroso- immunoglobulin; the immunoglobulin may  
be e.g. IgG, IgA, IgM, IgD or IgE; (B) a comps. comprising S-  
**nitroso -haemoglobin**; (E) a comps. comprising  
S-nitroso -myoglobin; (F) regulating protein or aminoacid function  
in an animal comprising administering a nitrosylating cpd., e.g.  
nitroglycerin, nitrosothiols or nitric oxide; (G) preventing  
cellular uptake of proteins in an animal comprising administering a  
nitrosylating cpd.; (H) regulating the function proteins in which a  
thiol is bound to a methyl gp.; (I) regulating the function of a  
protein which lacks a free thiol gp.; (J) regulating cellular  
function, comprising S-nitrosylation of a protein which is a  
cellular component or any protein which affects cellular function;  
(K) delivering nitric oxide to specific, targeted sites in the body  
of an animal comprising administering a comps. comprising e.g.  
S-nitroso-enzyme; (L) (i) inhibiting platelet function, (ii) causing  
vasodilation, (iii) relaxing smooth muscle, (iv) regulating cellular  
function or (v) delivering nitric oxide to specific, targeted sites  
in the body; (M) (i) inhibiting platelet function in an animal, (ii)  
causing vasodilation in an animal; (iii) treatment or prevention of  
cardiovascular disorders in an animal, (iv) relaxing non-vascular  
smooth muscle in an animal, (v) treatment or prevention of  
respiratory disorders in an animal or (vi) delivering nitric oxide  
to specific, targeted sites in the body of an animal, comprising  
administering a comps. comprising a S-nitroso -protein.

USE/ADVANTAGE - Used for the treatment and prevention of e.g.  
thrombosis, myocardial infarction, pulmonary embolism, stroke,  
atherosclerosis, hypoxic disorders, emphysema, asthma, bronchitis,  
fibrosis, acute respiratory distress syndrome, renal failure,  
gastrointestinal disease etc..  
Dwg.0/30

L8 ANSWER 6 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 91-040145 [06] WPIDS

DNC C91-017282

TI Indo phenyl-alpha-glycoside used for assaying alpha-amylase activity  
- prepd. by reaction of 4-aminophenol-alpha-glycoside with quinone  
deriv..

DC B03 B04 D16

PA (FUJF) FUJI PHOTO FILM CO LTD  
CYC 1  
PI JP 02306990 A 901220 (9106)\*  
ADT JP 02306990 A JP 89-128089 890522  
PRAI JP 89-128089 890522  
AB JP02306990 A UPAB: 930928

Indophenyl-alpha-glycoside of formula (I) is claimed. In (I) (X1-X6 are H, halogen, nitro, cyano, azido, acyl, sulphonic acid, **nitroso**, sulphonyl, sulphonyl, thiocyanate, isothiocyanate, isonitrile, imino, azo, diazo, alkyl, allyl or aryl; X3 and X4 and/or X5 and X6 may connect to form a condensed aromatic ring; n is No. 0-8. (I) is prepd. by reaction of 4-aminophenyl-alpha-glycoside of formula (II) with a quinone deriv. of formula (III).

USE/ADVANTAGE - When (I) is used disturbance by bilirubin or **hemoglobin** hardly occurs and a highly sensitive assay can be performed simply.

(I) is used as a substrate for the detection and quantitative analysis of amylase in the presence of alpha-glucosidase as coenzyme.

In an example, cpd. (I) 20 mmol., CaCl<sub>2</sub> 10 mmol. and alpha-glucosidase 500 units were dissolved in purified H<sub>2</sub>O, pH was adjusted at 6.9. Total vol. 20 ml. To 2 ml soln., sample serum 100 micro-l was added, warmed at 37 deg.C, and the change of absorbance at 610 nm was measured.

0/0

L8 ANSWER 7 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 86-002223 [01] WPIDS  
DNN N86-001594 DNC C86-000847  
TI Solid cyano-meth-haemoglobin reference material - from nitrosyl-penta cyano-ferrate with haemoglobin prepn. and opt. additives.  
DC B04 J04 S03  
IN MAGYARI, J  
PA (MEDK) MEDICOR MUEVEK  
CYC 1  
PI HU 36928 T 851028 (8601)\*  
ADT HU 36928 T HU 84-374 840127  
PRAI HU 84-374 840127  
AB HU 36928 T UPAB: 930922

Cyano-meth-haemoglobin is prepd. by reacting a cpd. contg. the nitrosyl-penta-cyano-ferrate- III -anion with a haemoglobin prepn. or a soln. of that prepn. in the presence of haemolysis enhancing surfactants and/or organic solvents and/or antimicrobial agents and/or stabilizers. The resulting soln. is finished to a dry prod. having any desired concn. of cyano-meth-haemoglobin.

The prod. is suitable for use as a reference material.

L8 ANSWER 8 OF 9 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 79-21002B [11] WPIDS  
TI Colouring ham or sausage - by admixing with nitrite and/or nitrate and browned haemoglobin, and heat treating.  
DC D12  
PA (NIIG) NIIGATA ENG CO LTD  
CYC 1  
PI JP 54017158 A 790208 (7911)\*  
PRAI JP 77-80736 770706

AB JP54017158 A UPAB: 930901  
Ham or sausage is prepd. by combining nitrile and/or nitrate with the material for ham and sausage and heat-treating the mixt. Improvement comprises adding browned hemoglobin to the material prior to the heat-treatment.

By the heat-treatment hemoglobin is converted to nitro-hemoglomogen through **nitrosohemoglobin** and nitrosohemoglomogen shows stable pink colour semi-permanently.

=> d que l9; d his l10

L9 6 SEA FILE=WPIDS ABB=ON (NITROS? OR NITRAT?) (2A) (HB OR HEMOGLOBIN# OR HAEMOGLOBIN#)

(FILE 'WPIDS' ENTERED AT 12:08:50 ON 24 JUN 1997)

L10 0 S L9 NOT L8

=> d que

L1 27 SEA FILE=WPIDS ABB=ON ("STAMLER J"/AU OR "STAMLER J S"/AU)

L2 6 SEA FILE=WPIDS ABB=ON (NITROS? OR NITRAT?) (2A) (HB OR HEMOGLOBIN# OR HAEMOGLOBIN#)

L3 3 SEA FILE=WPIDS ABB=ON NITROSYL? (2A) (HB OR HEMOGLOBIN# OR HAEMOGLOBIN#)

L4 3 SEA FILE=WPIDS ABB=ON NITROSOHB OR NITROSOHAEMOGLOBIN# OR NITROSYLHAEMOGLOBIN# OR SNOHB OR NOHB OR (NITROSYL OR NITROSO) (2W) (HAEMOGLOBIN# OR HEMOGLOBIN#)

L6 QUE ABB=ON NITROSOHB/OBI OR NITROSOHEMOGLOBIN#/OBI OR SNOHB/OBI OR S NOBH/OBI

L7 QUE ABB=ON (NITROSO/OBI OR NITROSYL/OBI) (L) (HB/OBI OR HEMOGLOBIN#/OBI)

L8 QUE ABB=ON NITROSYLHEMOGLOBIN/OBI OR NITROSYLHB/OBI

L10 5 SEA FILE=WPIDS ABB=ON L8 OR L7 OR L6

L11 9 SEA FILE=WPIDS ABB=ON L10 OR L4 OR L3 OR L2

L12 5 SEA FILE=WPIDS ABB=ON L1 AND L11

L13 6 SEA FILE=WPIDS ABB=ON L1 AND (HAEMOGLOBIN# OR HEMOGLOBIN#)

L14 6 SEA FILE=WPIDS ABB=ON L13 OR L12

=> d bib ab 1-6

L14 ANSWER 1 OF 6 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 97-212535 [19] WPIDS

CR 97-202348 [18]; 97-212491 [18]

DNC C97-068560

TI **Nitrosated or nitrated haemoglobin(s)**,  
their prepn. and uses - e.g. to oxygenate, to scavenge free radicals or release nitric oxide gps. to tissues and treat ischaemic injury, hypertension, angina.

DC B04 B05 D22

IN **STAMLER, J S**

PA (UYDU-N) UNIV DUKE MEDICAL CENT

CYC 74

PI WO 9710265 A1 970320 (9719)\* EN 83 pp

RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA  
PT SD SE SZ UG

W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI  
GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA  
UG US UZ VN

ADT WO 9710265 A1 WO 96-US14659 960913

PRAI US 96-667003 960620; US 95-3801 950915; US 96-616371 960315

AB WO 9710265 A UPAB: 970512

Delivering nitro-oxide to in a mammal comprises administering a low molecular weight nitrosating agent to the mammal.

Also claimed are: (1) a method for preparing **S-nitroso-haemoglobin** (SNO-Hb)(FeII) specifically S-nitrosylated on thiol groups, by incubating excess nitrosating agent with purified Hb in the absence of O<sub>2</sub>;

(2) a method for preparing SNO-Hb(FeII) O<sub>2</sub>, specifically S-nitrosylated on thiol groups (without oxidation of heme Fe) by incubating excess nitrosating agent with purified Hb in the presence of O<sub>2</sub>;

(3) a method for regulating delivery of O<sub>2</sub> and NO, in various redox forms, by administering a mixture of a low molecular weight thiol or **nitroso-thiol** and Hb or **nitrosated Hb**;

(4) use of a blood substitute comprising **nitrosated Hb** for delivering NO, for scavenging oxygen free radicals and NO and reducing blood pressure;

(5) a blood substitute comprising **nitrosated** or **nitrated Hb** and its uses;

(6) a method for regulating platelet activation by admin. of a composition comprising a substance (II) which controls the allosteric equilibrium or spin state of Hb;

(7) methods for forming poly-**nitrosated Hb** and poly-**nitrated Hb** (see 'Preferred Method'), and

(8) a composition comprising poly-**nitrosated Hb**.

USE - The method is used to increase the O<sub>2</sub> delivery capacity of Hb in a mammal suffering from shock, angina, stroke, reperfusion injury, acute lung injury, sickle cell anaemia and infection of red blood cells.

**S-nitroso-thiol** (RSNO) can be used to treat a blood borne disease (e.g. malaria) by isolating red blood cells, treating them with RSNO and re-administering them to the patient.

**Nitrosated** or **nitrated Hb** can be used to treat heart, brain, vascular and lung diseases; atherosclerosis and inflammation; also diseases resulting from platelet activation or adherence (e.g. myocardial infarction, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, sepsis and unstable angina).

**Nitrosated Hb** can also be used to treat stroke, angina, respiratory distress syndrome, and diseases or conditions with abnormalities of NO and oxygen metabolism (e.g. heart and lung diseases, sickle-cell anaemia, stroke, sepsis and organ transplantation); and to prevent thrombus formation.

**Nitrosated Hb** is also used to keep organs alive ex vivo to use for transplantation (all claimed).  
Dwg.0/11



AN 97-202348 [18] WPIDS  
 CR 97-212491 [18]; 97-212535 [18]  
 DNN N97-167201 DNC C97-064778  
 TI Method for measuring **nitrosyl** iron (II)  
**haemoglobin** in blood - or assaying nitric oxide prodn. in  
 disease states, e.g. septic shock, cardiogenic shock,  
 atherosclerosis, thrombosis and pulmonary hypertension.  
 DC B04 S03  
 IN **STAMLER, J S**  
 PA (UYDU-N) UNIV DUKE MEDICAL CENT  
 CYC 74  
 PI WO 9710493 A1 970320 (9718)\* EN 19 pp  
 RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA  
 PT SD SE SZ UG  
 W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI  
 GB GE HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG  
 MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA  
 UG US UZ VN  
 ADT WO 9710493 A1 WO 96-US14660 960913  
 PRAI US 96-616259 960315; US 95-3801 950915  
 AB WO 9710493 A UPAB: 970516  
 Method of measuring **nitrosyl** Fe(II)-**haemoglobin**  
 in blood or assaying nitric oxide prodn. in disease states  
 comprises: (a) lysing the red blood cells of a blood sample; (b)  
 prepg. a protein fraction of the lysed red blood cells; (c)  
 subjecting a protein fraction to photolysis; and (d) quantitating  
 the amt. of nitric oxide in the protein fraction by measuring a  
 chemiluminescence signal generated by a chemical reaction between  
 nitric oxide and ozone.  
 USE - Nitric oxide levels can be monitored in disease states,  
 e.g. septic shock, cardiogenic shock, hypovolemic shock,  
 atherosclerosis, hyperhomocysteinemia, venous thrombosis, arterial  
 thrombosis, coronary occlusion, pulmonary embolism, cerebrovascular  
 accidents, vascular fibrosis, ectopic lentis, osteoporosis, mental  
 retardation, skeletal deformities, pulmonary hypertension,  
 malignancy, infections, inflammation, asthma, tolerance to narcotics  
 and central nervous system disorders.  
 ADVANTAGE - The method is more sensitive than previous methods  
 using electron paramagnetic resonance.  
 Dwg.0/0  
 L14 ANSWER 3 OF 6 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
 AN 96-454984 [45] WPIDS  
 DNC C96-142594  
 TI Blood substitute compsns. used for e.g. treating cardiovascular  
 disorders - comprising, e.g. **haemoglobin** which is directly  
 or indirectly linked to a nitrosyl gp..  
 DC B04  
 IN **STAMLER, J**  
 PA (BGHM) BRIGHAM & WOMENS HOSPITAL  
 CYC 20  
 PI WO 9630006 A1 961003 (9645)\* EN 131 pp  
 RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE  
 W: AU CA JP  
 AU 9653682 A 961016 (9706)  
 ADT WO 9630006 A1 WO 96-US3866 960325; AU 9653682 A AU 96-53682 960325  
 FDT AU 9653682 A Based on WO 9630006

PRAI US 95-409720 950324

AB WO 9630006 A UPAB: 961111

A cpd. comprising a blood substitute to which an NO or NO<sub>2</sub> gp. is directly or indirectly linked. Also claimed is a blood substitute compsn. comprising the cpd. described above and a carrier.

The blood substitute is a haem protein, such as an opt. modified human or bovine **haemoglobin**. the cpd. is an S-nitroso, N-nitroso, O-nitroso or C-nitroso cpd. The blood substitute compsn. also comprises an additional component selected from phospholipids, nonionic surfactants, emulsifiers, and fatty acids.

USE - The nitrosylated blood substituents may be used for effecting vasodilation, platelet inhibition of thrombolysis, and for treating cardiovascular disorders. The blood substitute compsns. may also be used to maintain and perfuse transplant organs during transport. Other nitrosylated cpds., such as S-nitroso-albumin, may be used for causing relaxation of airway smooth muscle and for treatment of e.g. respiratory disorders. Admin. of the cpds. is e.g. oral or parenteral.

ADVANTAGE - **Nitrosylation of haemoglobin** increases **haemoglobin**-oxygen binding and can thus lead to an increase in the oxygen-carrying capacity of the blood.  
Dwg.1/33

L14 ANSWER 4 OF 6 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD

AN 94-332842 [41] WPIDS

DNN N94-261274 DNC C94-151360

TI Admin of e.g. nitric oxide by inhalation - is useful for treatment of pulmonary emboli, angina pectoris, acute respiratory distress syndrome, etc..

DC B05 B06 B07 P34

IN FROSTELL, C G; HEDENSTIERNA, G; HOGMAN, M E; LOSCALZO, J;  
**STAMLER, J S**; FROSTELL, C

PA (BGHM) BRIGHAM & WOMENS HOSPITAL

CYC 3

PI WO 9422499 A1 941013 (9441)\* EN 28 pp

AU 9464968 A 941024 (9505)

US 5427797 A 950627 (9531) 7 pp

EP 692984 A1 960124 (9609) EN

JP 09500609 W 970121 (9713) 19 pp

ADT WO 9422499 A1 WO 94-US3561 940331; AU 9464968 A AU 94-64968 940331;  
US 5427797 A US 93-43653 930406; EP 692984 A1 EP 94-912377 940331,  
WO 94-US3561 940331; JP 09500609 W JP 94-522387 940331, WO 94-US3561  
940331

FDT AU 9464968 A Based on WO 9422499; EP 692984 A1 Based on WO 9422499;  
JP 09500609 W Based on WO 9422499

PRAI US 93-43653 930406

AB WO 9422499 A UPAB: 941206

The following are claimed: (A) methods for (i) systemic prevention or treatment of systemic blood platelet aggregation and coagulation, (ii) prevention or treatment of acute coronary syndromes including angina pectoris or (iii) prevention or treatment of acute respiratory distress syndrome, comprising admin., by the inhalation route, of a cpd. selected from nitric oxide and cpds. that deliver nitric oxide upon admin..

Also claimed is prevention or treatment of pulmonary emboli comprising admin., to the lung, of a pharmaceutical compsn.

comprising a cpd. selected from nitric oxide and cpds. which deliver nitric oxide upon admin..

Dosage is 1 pg-1 mg per kg of body wt.

Dwg.0/1

L14 ANSWER 5 OF 6 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
 AN 93-214031 [26] WPIDS  
 CR 92-366158 [44]  
 DNC C93-094926  
 TI S-nitroso thiol smooth muscle relaxants - used e.g. for treating respiratory disorders or impotence, and for improving oxygen transport in body tissue.  
 DC B05  
 IN BROWN, R; DRAZEN, J; LOSCALZO, J; SIMON, D; SLIVKA, A; **STAMLER, J**  
 PA (BGHM) BRIGHAM & WOMENS HOSPITAL  
 CYC 2  
 PI WO 9312068 A1 930624 (9326)\* EN 74 pp  
 AU 9332371 A 930719 (9344)  
 US 5380758 A 950110 (9508) 35 pp  
 US 5574068 A 961112 (9651) 37 pp  
 ADT WO 9312068 A1 WO 92-US10447 921207; AU 9332371 A AU 93-32371 921207; US 5380758 A CIP of US 91-676691 910329, CIP of US 91-804665 911211, US 92-943834 920914; US 5574068 A CIP of US 91-676691 910329, CIP of US 91-804665 911211, Cont of US 92-943834 920914, US 94-338893 941114  
 FDT AU 9332371 A Based on WO 9312068; US 5574068 A Cont of US 5380758  
 PRAI US 92-943834 920914; US 91-804665 911211; US 91-676691 910329; US 94-338893 941114  
 AB WO 9312068 A UPAB: 931116  
 Methods involving admin. of S-nitrosothiol cpds. (I) are claimed for: relaxing airway, gastrointestinal, corpus cavernosum, bladder or uterine smooth muscle; treating or preventing respiratory disorders (esp. obstructive lung disease, emphysema, asthma, bronchitis, fibrosis, excessive mucous secretion, air flow obstruction or lung disorders from post-surgical complications); alleviating contraction or spasm of gastrointestinal smooth muscle associated with endoscopic procedures; treating or preventing impotence; increasing the capacity of **haemoglobin** to bind oxygen; increasing oxygen transport to body tissues; and treating or preventing disorders associated with insufficient oxygen to body tissues.  
 S-Nitrosothiol cpds. of formula Y-(CH<sub>2</sub>)<sub>x</sub>-SNO (I) are new: Ub (I) x = 2-20; T = CH<sub>3</sub>, SH, F, 1-6C alkoxy, CN, carboxamido, 3-6C cycloalkyl, aralkoxy, 2-6C alkylsulphinyl, arylthio, 1-6C alkylamino, 2-15C dialkylamino, OH, carbamoyl, 1-6C N-alkylcarbamoyl, 2-15C N,N-dialkylcarbamoyl, NH<sub>2</sub>, COOH, H, NO<sub>2</sub>, or aryl (where aryl includes benzyl, naphthyl and anthracenyl).  
 USE/ADVANTAGE - (I) have a potent relaxant effect, mediated both by guanylate cyclase and a cGMP-independent mechanism, on non-vascular smooth muscle. They also increase the binding affinity between **haemoglobin** and oxygen. Further disorders treated with (I) are e.g. bladder dysfunction and premature labour. (I) facilitate diagnostic instrumentation procedures such as endoscopy, laparoscopy, bronchoscopy and cystoscopy. (I) supply NO in a biologically active, stable and non-toxic form. As bronchodilatory, (I) do not have the side-effects of beta-agonists and methyl xanthines. They also mediate the activity of vasoactive intestinal

peptide. Administration of (I) is oral, sublingual, intravenous, topical, intramuscular or as aerosol.  
Dwg.0/19

L14 ANSWER 6 OF 6 WPIDS COPYRIGHT 1997 DERWENT INFORMATION LTD  
AN 93-182246-22 WPIDS  
DNC C93-080681  
TI Proteins comprising nitrosylated sulphur-hydrogen gps. e.g.  
S-nitroso-T-PA - regulate protein and cellular functions, for  
treating and preventing emphysema, asthma, bronchitis, fibrosis  
etc..  
DC B04 D16  
IN LOSCALZO, J; SIMON, D; SINGEL, D; STAMLER, J  
PA (BGHM) BRIGHAM & WOMENS HOSPITAL  
CYC 2  
PI WO 9309806 A1 930527 (9322)\* EN 114 pp  
AU 9230715 A 930615 (9340)  
EP 676964 A1 951018 (9546) EN  
US 5593876 A 970114 (9709) 58 pp  
ADT WO 9309806 A1 WO 92-US9667 921113; AU 9230715 A AU 92-30715 921113;  
EP 676964 A1 EP 92-924388 921113, WO 92-US9667 921113; US 5593876 A  
CIP of US 91-791668 911114, Div ex US 92-943835 920914, Div ex US  
94-198854 940217, US 94-287830 940809  
FDT AU 9230715 A Based on WO 9309806; EP 676964 A1 Based on WO 9309806  
PRAI US 92-943835 920914; US 91-791668 911114; US 94-198854 940217;  
US 94-287830 940809  
AB WO 9309806 A UPAB: 931115  
The following are claimed: (A) a cpd. comprising S-nitroso-enzyme;  
the enzyme may be e.g. tissue-type plasminogen activator (tPA),  
streptokinase, urokinase or cathepsin; (B) a cpd. comprising  
S-nitroso -lipoprotein; the lipoprotein may be e.g. chylomicrons,  
very low density lipoprotein or high-density lipoprotein; (C) a  
compsn. comprising S-nitroso- immunoglobulin; the immunoglobulin may  
be e.g. IgG, IgA, IgM, IgD or IgE; (B) a compsn. comprising S-  
**nitroso -haemoglobin**; (E) a compsn. comprising  
S-nitroso -myoglobin; (F) regulating protein or aminoacid function  
in an animal comprising administering a nitrosylating cpd., e.g.  
nitroglycerin, nitrosothiols or nitric oxide; (G) preventing  
cellular uptake of proteins in an animal comprising administering a  
nitrosylating cpd.; (H) regulating the function proteins in which a  
thiol is bound to a methyl gp.; (I) regulating the function of a  
protein which lacks a free thiol gp.; (J) regulating cellular  
function, comprising S-nitrosylation of a protein which is a  
cellular component or any protein which affects cellular function;  
(K) delivering nitric oxide to specific, targeted sites in the body  
of an animal comprising administering a compsn. comprising e.g.  
S-nitroso-enzyme; (L) (i) inhibiting platelet function, (ii) causing  
vasodilation, (iii) relaxing smooth muscle, (iv) regulating cellular  
function or (v) delivering nitric oxide to specific, targeted sites  
in the body; (M) (i) inhibiting platelet function in an animal, (ii)  
causing vasodilation in an animal; (iii) treatment or prevention of  
cardiovascular disorders in an animal, (iv) relaxing non-vascular  
smooth muscle in an animal, (v) treatment or prevention of  
respiratory disorders in an animal or (vi) delivering nitric oxide  
to specific, targeted sites in the body of an animal, comprising  
administering a compsn. comprising a S-nitroso -protein.

USE/ADVANTAGE - Used for the treatment and prevention of e.g.

Celsa 08/616,371

thrombosis, myocardial infarction, pulmonary embolism, stroke,  
atherosclerosis, hypoxic disorders, emphysema, asthma, bronchitis,  
fibrosis, acute respiratory distress syndrome, renal failure,  
gastrointestinal disease etc..

Dwg.0/30

=> fil medline

FILE 'MEDLINE' ENTERED AT 12:28:13 ON 24 JUN 1997

FILE LAST UPDATED: 20 JUN 1997 (19970620/UP). FILE COVERS 1966 TO DATE.  
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MEDLINE ANNUAL RELOAD AVAILABLE ON STN IN RECORD TIME (2/08/97).  
ENTER HELP RLOAD FOR DETAILS.

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SUBSTANCE IDENTIFICATION.

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(FILE 'MEDLINE' ENTERED AT 12:13:03 ON 24 JUN 1997)

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L1 379 SEA FILE=MEDLINE ABB=ON "STAMLER J"/AU OR "STAMLER J S"/  
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L2 2881 S NITROSO COMPOUNDS/CT  
L3 54752 S HEMOGLOBINS+NT/CT  
L4 13 S L1 AND L2  
L5 2 S L1 AND L3  
L6 14 S L4 OR L5  
L7 98 S L2 AND L3  
L8 28 S L7 AND NITRIC OXIDE/CT  
L9 15484 S FREE RADICALS/CT OR FREE RADICAL SCAVENGERS/CT  
L10 17432 S L9 OR FREE RADICAL SCAVENGERS/CT  
L11 5 S L10 AND L7  
L12 11 S L8 AND RELEAS?  
L13 11 S L12 AND (NO OR NITRIC OXIDE) (4A) RELEAS?  
E BLOOD PRESSURE/CT  
E E3\_ALL  
E BLOOD PRESSURE/CT  
E E3+ALL  
L14 234170 S BLOOD PRESSURE+NT/CT OR HYPERTENSION+NT/CT  
L15 2 S L14 AND L7  
E THIOLS/CT  
L16 13283 S SULFHYDRYL COMPOUNDS/CT  
L17 8 S L16 AND L7  
L18 13 S L11 OR L15 OR L17  
L19 4 S L7 AND (L2 (L) TU./CT)  
L20 1 S (DISEASE# OR SICKLE CELL)AND L7  
L21 0 S L7 AND (L3 (L) TU./CT)  
L22 14 S L20 OR L18  
L23 13 S L6 NOT L22

FILE 'MEDLINE' ENTERED AT 12:28:13 ON 24 JUN 1997

=> d .med 122 1-14; d bib ab 123 1-13

L22 ANSWER 1 OF 14 MEDLINE

AN 97288390 MEDLINE

TI Effect of thiol status on nitric oxide metabolism in the circulation.

AU Minamiyama Y; Takemura S; Inoue M

CS Department of Biochemistry, Osaka City University Medical School, Japan.

SO ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1997 May 1) 341 (1) 186-92.

Journal code: 6SK. ISSN: 0003-9861.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9708

EW 19970801

AB To elucidate the dynamics of nitric oxide (NO) metabolism in the circulation and its relationship with glutathione metabolism, formation of nitrosylhemoglobin (NO-Hb), S-nitrosothiols (RSNO), and nitrite+nitrate (NOx) was determined in blood samples from normal rats and animals that were treated with a loading dose of GSH or L-buthionine-[S,R]-sulfoximine (BSO), a specific inhibitor of GSH synthesis. When incubated in vitro with 0.2 mM NOC7, an NO donor, NO-Hb levels increased rapidly, peaked at 10 min, and decreased thereafter with a half-life of 35 min in blood samples from control, BSO-treated, or GSH-loaded animals. Levels of low-molecular-weight RSNO in plasma samples from the three animal groups also increased transiently, peaked at 10 min, and decreased thereafter. However, the amount of RSNO formed in GSH-loaded rat plasma was significantly greater than in control and BSO-treated animals. Plasma levels of NOx rapidly and similarly increased in all animal groups. Intravenously injected NOC7 also generated NO-Hb in circulating erythrocytes. In control animals, blood levels of NO-Hb increased maximally at 30 min and decreased thereafter with a half-life of 100 min. NO-Hb formed in the GSH-loaded group was significantly lower than in the control group. In contrast, the rate of NO-Hb formation was significantly higher with the BSO-treated group than with the control group. Although NOC7 did not affect the plasma levels of low-molecular-weight RSNO in plasma of both control and BSO-treated groups, it significantly increased RSNO in the GSH-loaded group. Thirty minutes after administration of NOC7, about 20% of the dose was recovered as plasma NOx in all animal groups. These results suggested that GSH status in animals might affect the metabolism of NO.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't

Buthionine Sulfoximine: BL, blood

Buthionine Sulfoximine: PD, pharmacology

Electron Spin Resonance Spectroscopy

Glutathione: AA, analogs & derivatives

\*Glutathione: BL, blood

Glutathione: PD, pharmacology

**Hemoglobins: ME, metabolism**

Nitrates: BL, blood

\*Nitric Oxide: BL, blood

Nitrites: BL, blood

**Nitroso Compounds: BL, blood**

Rats

Rats, Wistar

**\*Sulphydryl Compounds: BL, blood**

Triazenes: PD, pharmacology

L22 ~~ANSWER 2 OF 14~~ MEDLINE

AN 97218126 MEDLINE

TI Formation of peroxide- and globin-derived radicals from the reaction of methaemoglobin and metmyoglobin with t-butyl hydroperoxide: an ESR spin-trapping investigation.

AU Van der Zee J

CS Department of Medical Biochemistry, Leiden University, The Netherlands.

SO BIOCHEMICAL JOURNAL, (1997 Mar 1) 322 ( Pt 2) 633-9.

Journal code: 9YO. ISSN: 0264-6021.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9706

EW 19970602

AB The reaction of human methaemoglobin and horse metmyoglobin with t-butyl hydroperoxide (t-BuOOH) was investigated with the ESR spin-trapping technique. With the spin trap 5,5-dimethyl-1-pyrroline N-oxide (DMPO) the formation of peroxy, alkoxy and methyl radicals derived from t-BuOOH could be detected. The relative contributions of these radicals were determined at various DMPO concentrations by computer simulation. From these data it could be concluded that the alkoxy radical was the initial radical produced, which indicates that the hydroperoxide is cleaved homolytically. Further investigations, with the nitroso spin trap 2-methyl-2-nitrosopropane (MNP), showed the formation of globin-centred radicals. Non-specific proteolysis of the MNP adducts revealed isotropic three-line spectra, which means that the radical adducts were centred on a tertiary carbon with no bonds to a hydrogen or nitrogen. Comparison with MNP adducts of several amino acids indicated that in methaemoglobin the radical adduct was most probably located on a valine residue. With metmyoglobin the same adduct was obtained, whereas an additional adduct could be assigned to a tyrosyl radical. These protein radicals most probably resulted from hydrogen abstraction by the metal-oxo species, formed by heterolytic cleavage of the hydroperoxide. These results therefore show that homolytic cleavage of the hydroperoxide leads to the formation of peroxide-derived radicals, whereas concurrent heterolytic cleavage results in protein-derived radicals.

CT Amino Acids: CH, chemistry

Cold

Computer Simulation

Cyclic N-Oxides

Electron Spin Resonance Spectroscopy

**Free Radicals**

**\*Globin: CH, chemistry**

Hydroxyl Radical

**\*Methemoglobin: CH, chemistry**

**\*Metmyoglobin: CH, chemistry**

Models, Chemical

**Nitroso Compounds: CH, chemistry**

Oxidation-Reduction  
 \*Peroxides: CH, chemistry  
 Spin Labels  
 Valine: CH, chemistry

~~L22 ANSWER 3 OF 14 MEDLINE~~

AN 97127534 MEDLINE  
 TI Haemoglobin adducts of N-nitroso compounds.  
 AU Richter E  
 CS Walther-Straub-Institut fur pharmakologie und Toxikologie,  
 Ludwig-Maximilians-Universitat Munchen, Germany.  
 SO EUROPEAN JOURNAL OF CANCER PREVENTION, (1996 Sep) 5 Suppl 1 115-9.  
 Ref: 32  
 Journal code: BNN. ISSN: 0959-8278.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Priority Journals  
 EM 9705  
 EW 19970502  
 CT Check Tags: Animal; Human  
 \*Carcinogens: AE, adverse effects  
 Carcinogens: ME, metabolism  
**Disease Models, Animal**  
 \*DNA Adducts: AN, analysis  
 DNA Damage: DE, drug effects  
**\*Hemoglobins: AN, analysis**  
 \*Neoplasms: ET, etiology  
**\*Nitroso Compounds: AE, adverse effects**  
**Nitroso Compounds: ME, metabolism**  
 \*Smoking: AE, adverse effects  
 \*Tumor Markers, Biological: AN, analysis

~~L22 ANSWER 4 OF 14 MEDLINE~~

AN 97032789 MEDLINE  
 TI Cyclic GMP elevation by 5-hydroxytryptamine is due to nitric oxide  
 derived from endogenous nitrosothiol in NG108-15 cells.  
 AU Arima T; Ohshima Y; Mizuno T; Kitamura Y; Segawa T; Nomura Y  
 CS Department of Pharmacology, Faculty of Pharmaceutical Sciences,  
 Hokkaido University, Sapporo, Japan.  
 SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Oct 14)  
 227 (2) 473-8.  
 Journal code: 9Y8. ISSN: 0006-291X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 9702  
 EW 19970204  
 AB To clarify the involvement of nitric oxide (NO) derived from  
 nitrosothiols (RSNO) in 5-hydroxytryptamine (5-HT)-induced  
 Ca(2+)-independent cGMP formation (CIGF) in NG108-15 cells, we  
 investigated the effects of 5-HT on intracellular contents of RSNO  
 as well as of NO metabolites. 5-HT stimulation resulted in an  
 increase in the intracellular contents of nitrate and cGMP. RSNO was



detected in NG108-15 cells and was decreased by 5-HT stimulation. Furthermore, the time course of nitrate increase was coincident with that of RSNO decrease. CarboxyPTIO inhibited 5-HT-induced CIGF, whereas oxyhemoglobin failed to inhibit it. The data suggest that NO is stored in a stable form as RSNO and that 5-HT stimulates NO generation from endogenous RSNO, which is followed by elevation of cGMP via activation of cytosolic guanylyl cyclase by NO in NG108-15 cells. We suggest the existence of a novel 5-HT signal transduction pathway involved in NO generation in NG108-15 cells.

CT Check Tags: Animal

\*Cyclic GMP: PD, pharmacology

Glioma

Hybrid Cells

Kinetics

Neuroblastoma

Nitrates: AN, analysis

\*Nitric Oxide: PH, physiology

Nitrites: AN, analysis

Nitroprusside: PD, pharmacology

\*Nitroso Compounds: ME, metabolism

Oxyhemoglobins: PD, pharmacology

\*Serotonin: PD, pharmacology

\*Sulfhydryl Compounds: ME, metabolism

L22 ~~ANSWER 5 OF 14 MEDLINE~~

AN 96207749 MEDLINE

TI S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control [see comments].

CM Comment in: Nature 1996 Mar 21;380(6571):205

Comment in: Nature 1996 Sep 5;383(6595):30-1

AU Jia L; Bonaventura J; Stamler J S

CS Department of Medicine, Divisions of Respiratory and Cardiovascular Medicine, Duke University Medical Center, Durham, NC 27710, USA.

SO NATURE, (1996 Mar 21) 380 (6571) 221-6.

Journal code: NSC. ISSN: 0028-0836.

CY ENGLAND: United Kingdom

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Cancer Journals; Priority Journals

EM 9609

AB A dynamic cycle exists in which haemoglobin is S-nitrosylated in the lung when red blood cells are oxygenated, and the NO group is released during arterial-venous transit. The vasoactivity of S-nitrosohaemoglobin is promoted by the erythrocytic export of S-nitrosothiols. These findings highlight newly discovered allosteric and electronic properties of haemoglobin that appear to be involved in the control of blood pressure and which may facilitate efficient delivery of oxygen to tissues. The role of S-nitrosohaemoglobin in the transduction of NO-related activities may have therapeutic applications.

CT Check Tags: Animal; Human; Support, U.S. Gov't, P.H.S.

Allosteric Regulation

\*Blood Pressure: PH, physiology

Cysteine: PH, physiology

\*Erythrocytes: PH, physiology

\*Hemoglobins: PH, physiology

Nitric Oxide: PH, physiology

**Nitroso Compounds: BL, blood**  
**\*Nitroso Compounds: ME, metabolism**  
 Oxygen: BL, blood  
 Rats  
 Rats, Sprague-Dawley  
**Sulphydryl Compounds: BL, blood**  
 Vasoconstriction: PH, physiology

~~L22 ANSWER 6 OF 14 MEDLINE~~

AN 96175199 MEDLINE  
 TI Hemoglobin reveals new role as blood pressure regulator [news].  
 AU Glanz J  
 SO SCIENCE, (1996 Mar 22) 271 (5256) 1670.  
 Journal code: UJ7. ISSN: 0036-8075.  
 CY United States  
 DT News Announcement  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 9606  
 CT Check Tags: Animal

**\*Blood Pressure: PH, physiology**  
 Cysteine: ME, metabolism  
**Hemoglobins: CH, chemistry**  
**\*Hemoglobins: ME, metabolism**  
 Nitric Oxide: BL, blood  
 \*Nitric Oxide: ME, metabolism  
**Nitroso Compounds: ME, metabolism**  
 Rats  
 Vasoconstriction

L22 ANSWER 7 OF 14 MEDLINE

AN 95284053 MEDLINE  
 TI Role of thiols in the targeting of S-nitroso thiols to red blood cells.  
 AU Pietraforte D; Mallozzi C; Scorza G; Minetti M  
 CS Laboratorio di Biologia Cellulare, Istituto Superiore di Sanit`a, Roma, Italy..  
 SO BIOCHEMISTRY, (1995 May 30) 34 (21) 7177-85.  
 Journal code: A0G. ISSN: 0006-2960.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 9509  
 AB We compared the nitric oxide (.NO)-releasing characteristics of two NO donors, the S-nitroso adduct of bovine serum albumin (BSANO) and the S-nitroso adduct of L-glutathione (GSNO). In oxygenated phosphate buffer (pH 7.4) and in hemoglobin solution, both NO donors released .NO only in the presence of a low molecular weight thiol (the most active was L-cysteine). The requirement of thiol to release .NO strongly suggests that a transnitrosation reaction occurs between the S-nitroso adduct of the NO donor and the sulphydryl group of the NO acceptor. The reaction produced a labile S-nitroso-L-cysteine intermediate that released .NO. As shown by spin-trapping experiments, the transnitrosation reaction involved the formation of .NO (trapped by 2-(4-carboxyphenyl)-4,4,5,5-tetramethylimidazoline-1-oxyl 3-oxide) and .S radicals (trapped by

5,5'-dimethyl-1-pyrroline N-oxide) of both the NO donors and the NO acceptor (L-cysteine). The reaction leading to .S radical formation was distinct from the transnitrosation reaction, since it was oxygen-dependent. We suggest that .S radicals are formed from oxidizing species produced after a reaction between .NO and molecular oxygen (.NO<sub>2</sub> is a likely candidate). As for pure .NO gas, the major oxidation product of NO donors, in phosphate buffer (pH 7.4), was NO<sub>2</sub><sup>-</sup>, with no formation of NO<sub>3</sub><sup>-</sup>. In the presence of oxyhemoglobin, both NO donors produced only NO<sub>3</sub><sup>-</sup>. BSANO and GSNO showed distinct patterns of .NO release both in phosphate buffer and in the presence of hemoglobin. (ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Human; Support, Non-U.S. Gov't

Buffers

Electron Spin Resonance Spectroscopy

\*Erythrocytes: ME, metabolism

**Free Radical Scavengers**

**Free Radicals**

**Hemoglobins: ME, metabolism**

**Methemoglobin: ME, metabolism**

Nitric Oxide: CH, chemistry

Nitric Oxide: ME, metabolism

\***Nitroso Compounds: ME, metabolism**

Oxidation-Reduction

Phosphates

Serum Albumin, Bovine: ME, metabolism

~~\*Sulfhydryl Compounds: PH, physiology~~

L22 ANSWER 8 OF 14 MEDLINE

AN 95177576 MEDLINE

TI Scavenging effects of hemoglobin and related heme containing compounds on nitric oxide, reactive oxidants and carcinogenic volatile nitrosocompounds of cigarette smoke. A new method for protection against the dangerous cigarette constituents.

AU Deliconstantinos G; Villiotou V; Stavrides J C

CS Department of Experimental Physiology, University of Athens, Medical School, Greece.

SO ANTICANCER RESEARCH, (1994 Nov-Dec) 14 (6B) 2717-26.

Journal code: 59L. ISSN: 0250-7005.

CY Greece

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9506

AB The present study refers to the utilization of hemoglobin and related heme containing substances in scavenging noxious compounds contained in the gas phase of cigarette smoke (e.g. nitric oxide (NO), nitrogen oxides (NO<sub>x</sub>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), carbon monoxide (CO), aldehydes, trace elements and carcinogenic nitrosocompounds) which were up to today insufficiently retained by conventional cigarette filters. Hemoglobin impregnated conventional cigarette filters were capable of withholding the above noxious components of the cigarette smoke up to 90%. Similar results were also obtained when solid hemoglobin was sandwiched between two common filters so that all cigarette smoke drawn through the filter comes into contact with the active groups of the hemoglobin molecules (Fe<sup>3+</sup>, Fe<sup>2+</sup>, -SH, -NH<sub>2</sub>). The present study also shows that noxious oxidants contained in cigarette smoke can be retained and

neutralized by appropriate scavengers like: a) substances which contain stereospecifically bound iron, b) substances which contain porphyrin ring with iron (e.g. protoporphyrin), c) substances which contain porphyrin ring that does not necessarily contain iron, d) substances which contain porphyrin ring complexed with other metals (e.g.  $\text{Cu}^{2+}$ ,  $\text{Mg}^{2+}$ ). We have also demonstrated that rat alveolar macrophages challenged by cigarette smoke release both superoxide ( $\text{O}_2^-$ ) and NO the interaction of which resulted in the formation of peroxynitrite ( $\text{ONOO}^-$ ). Alveolar macrophages continue to release  $\text{NO/ONOO}^-$  for 30 min following two or three puffs of smoke. Similar results were also obtained in experiments with human volunteers. It was shown that during cigarette smoking the ratio of  $\text{NO/ONOO}^-$  in the inhaled smoke was 1:0.5 while in the exhaled smoke was 1:9, due to secondary redox reactions taking place in the lung resulting in the  $\text{ONOO}^-$  formation. When smokers inhaled cigarette smoke passed through a conventional filter containing hemoglobin, a 70% reduction of both NO and  $\text{ONOO}^-$  in their exhaled cigarette smoke was observed. All findings prove conclusively that, alveolar macrophages exposed to cigarette smoke evoke a dramatic increase of NO,  $\text{NO}_x$ ,  $\text{ONOO}^-$  and  $\text{H}_2\text{O}_2$  inside the lung. These substances stimulate by a positive feed back mechanism the alveolar macrophages and perhaps even endothelium of the alveolar vessels, to produce more oxidants resulting in lung damage.

CT Check Tags: Human; Support, Non-U.S. Gov't

\*Anticarcinogenic Agents

\*Carcinogens

Carcinogens: AN, analysis

Chemiluminescence

**Free Radicals: AN, analysis**

\*Heme

\*Hemoglobins

Hydrogen Peroxide: AN, analysis

Iron

Kinetics

\*Nitric Oxide

Nitric Oxide: AN, analysis

\*Nitroso Compounds

**Nitroso Compounds: AN, analysis**

\*Reactive Oxygen Species

Reactive Oxygen Species: AN, analysis

\*Smoke: AE, adverse effects

Smoke: AN, analysis

\*Smoking: AE, adverse effects

Spectrophotometry

Time Factors

Trace Elements: AN, analysis

L22 ANSWER 9 OF 14 MEDLINE

AN 92119097 MEDLINE

TI Charge-shift strategy for isolation of hemoglobin-carcinogen adducts formed at the beta 93 cysteine sulfhydryl groups.

AU Haugen D A

CS Biological and Medical Research Division, Argonne National Laboratory, Illinois 60439-4833..

SO CHEMICAL RESEARCH IN TOXICOLOGY, (1989 Nov-Dec) 2 (6) 379-85.

Journal code: A5X. ISSN: 0893-228X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 9204  
 AB Qualitative and quantitative analysis of human hemoglobin-carcinogen adducts has potential as a diagnostic tool for estimation of biologically effective levels of carcinogen exposure and for attaining a better understanding of individual susceptibility to chemical carcinogenesis. The purpose of this study was to devise a strategy for preanalytical enrichment of the class of covalent human hemoglobin-carcinogen adducts formed by reaction at the hemoglobin beta 93 cysteine sulfhydryl groups. The results define a charge-shift strategy in which a mixture composed of natural hemoglobin (Hb-SH) and low levels of hemoglobin-S-xenobiotic adducts (Hb-SX) is treated with an anionic sulfhydryl reagent (R-), followed by anion-exchange liquid chromatographic separation of Hb-SR- from the unreactive Hb-SX adducts. Using 4-(iodoacetamido)-salicylic acid as the charge-shift reagent, we applied the strategy to the isolation of chromatographically similar adducts with either 4-nitrosobiphenyl or [3H]-N-ethylmaleimide. The strategy was effective for adduct concentrations less than or equal to 10 mumol/mol of hemoglobin. Application of the strategy provides an adduct-enriched fraction useful for subsequent analysis using either currently available techniques or alternate chemical or biochemical techniques that may be designed to take advantage of the enrichment procedure.

CT Check Tags: Human; In Vitro; Support, U.S. Gov't, Non-P.H.S.  
 Aminobiphenyl Compounds: PD, pharmacology  
 Biphenyl Compounds: PD, pharmacology  
 \*Carcinogens: CH, chemistry  
 Chromatography, Ion Exchange  
 \*Cysteine: CH, chemistry  
 Erythrocytes: DE, drug effects  
 Ethylmaleimide: PD, pharmacology  
 \*Hemoglobins: CH, chemistry  
 Hemoglobins: IP, isolation & purification  
 Hydrolysis  
 Indicators and Reagents  
 Iodoacetamide: AA, analogs & derivatives  
 Nitroso Compounds: PD, pharmacology  
 Salicylic Acids  
 Spectrophotometry, Ultraviolet  
 \*Sulfhydryl Compounds: CH, chemistry

L22 ANSWER 10 OF 14 MEDLINE  
 AN 90158535 MEDLINE  
 TI Aniline-, phenylhydroxylamine-, nitrosobenzene-, and nitrobenzene-induced hemoglobin thiol free radical formation in vivo and in vitro.  
 AU Maples K R; Eyer P; Mason R P  
 CS Laboratory of Molecular Biophysics, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina 27709..  
 SO MOLECULAR PHARMACOLOGY, (1990 Feb) 37 (2) 311-8.  
 Journal code: NGR. ISSN: 0026-895X.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)

LA English  
 FS Priority Journals; Cancer Journals  
 EM 9005  
 AB We have employed the ESR spin trapping technique in vivo to detect the formation of the 5,5-dimethyl-1-pyrroline-N-oxide (DMPO)/hemoglobin thiyl free radical adduct in the blood of rats following administration of either aniline, phenylhydroxylamine, nitrosobenzene, or nitrobenzene. This DMPO adduct was a six-line, strongly immobilized, radical adduct. Using rat red blood cells, both phenylhydroxylamine and nitrosobenzene were able to induce the formation of the DMPO/glutathiyl free radical adduct and the same DMPO/hemoglobin thiyl free radical adduct was detected in in vivo samples. In experiments using purified rat oxyhemoglobin, a four-line, weakly immobilized, DMPO/hemoglobin thiyl free radical adduct was detected, in addition to the six-line strongly immobilized adduct. When this study was repeated using human red blood cells, we detected only the DMPO/glutathiyl free radical adduct and, when purified human oxyhemoglobin was employed, only the four-line, weakly immobilized, DMPO/hemoglobin thiyl radical adduct could be detected. In a study using reduced glutathione, we found that phenylhydronitroxide free radicals were reduced by glutathione and that glutathione was concomitantly oxidized to its thiyl free radical. We propose that the species responsible for the oxidation of the thiols to yield the thiyl free radicals in vivo and in vitro was the phenylhydronitroxide radical produced from the reaction of phenylhydroxylamine with oxyhemoglobin.

CT Check Tags: Animal; Human; In Vitro; Male  
 \*Aniline Compounds: BL, blood  
 Cyclic N-Oxides: DU, diagnostic use  
 Electron Spin Resonance Spectroscopy  
 Erythrocytes: ME, metabolism  
**Free Radicals**  
 Glutathione: BL, blood  
**\*Hemoglobins: ME, metabolism**  
 \*Hydroxylamines: BL, blood  
 Models, Chemical  
 \*Nitrobenzenes: BL, blood  
**\*Nitroso Compounds: BL, blood**  
 Oxidation-Reduction  
**Oxyhemoglobins: ME, metabolism**  
 Rats  
 Rats, Inbred Strains  
 Spin Labels

L22 ANSWER 11 OF 14 MEDLINE  
 AN 85096220 MEDLINE  
 TI Analysis of hemoglobin as a dose monitor for alkylating and arylating agents.  
 AU Neumann H G  
 SO ARCHIVES OF TOXICOLOGY, (1984 Nov) 56 (1) 1-6.  
 Journal code: 8J7. ISSN: 0340-5761.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 8504  
 AB Genotoxic xenobiotics bind covalently to hemoglobin in vivo. The

major reaction product of aromatic amines is a sulfinic acid amide resulting from the reaction of aryl nitroso derivatives with SH-groups. Alkylating compounds react with cysteine, histidine and the terminal valine. The adducts are formed proportional to dose down to extremely small doses, they are stable throughout the life-span of the erythrocytes and accumulate upon repeated exposure. Methods for their determination in blood samples from experimental animals and humans are becoming available. Moreover, it has been demonstrated that for a given agent, a constant ratio exists between the reaction with tissue DNA and hemoglobin over a wide range of doses, which indicates that the reactions follow apparent first order kinetics. The extent of hemoglobin binding is therefore considered to be a relative measure of tissue dose, and should correlate much better with risk than exposure levels calculated from concentrations in the environment. Not only can the actual uptake be monitored more reliably, but also the individual's capacity to metabolically activate the absorbed agent. Biomonitoring of hemoglobin-bound metabolites represents a novel approach to control exposure to potential carcinogens, to correlate environmental exposure with tissue dose and eventually also with human risk.

CT Check Tags: Animal; Human; Support, Non-U.S. Gov't

\*Alkylating Agents: AE, adverse effects

Alkylating Agents: ME, metabolism

Amines: ME, metabolism

\*Carcinogens, Environmental: AE, adverse effects

Carcinogens, Environmental: ME, metabolism

Chemistry

Environmental Exposure

\*Hemoglobinometry

Hemoglobins: ME, metabolism

Nitroso Compounds: ME, metabolism

Protein Binding

Risk

Sulphydryl Compounds: ME, metabolism

L22 ANSWER 12 OF 14 MEDLINE

AN 80179129 MEDLINE

TI Possible involvement of S-nitrosothiols in the activation of guanylate cyclase by nitroso compounds.

AU Ignarro L J; Edwards J C; Gruetter D Y; Barry B K; Gruetter C A

SO FEBS LETTERS, (1980 Feb 11) 110 (2) 275-8.

Journal code: EUH. ISSN: 0014-5793.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 8009

CT Check Tags: Animal; Support, U.S. Gov't, P.H.S.

Acetylcysteine: AA, analogs & derivatives

Acetylcysteine: PD, pharmacology

Cattle

\*Coronary Vessels: EN, enzymology

Dithiothreitol: AA, analogs & derivatives

Dithiothreitol: PD, pharmacology

Enzyme Activation

Ferricyanides: PD, pharmacology

Glutathione: AA, analogs & derivatives

Glutathione: PD, pharmacology  
 \*Guanylate Cyclase: ME, metabolism  
 Kinetics  
 \*Liver: EN, enzymology  
 \*Methemoglobin: PD, pharmacology  
 Myoglobin: PD, pharmacology  
 \*Nitroso Compounds: PD, pharmacology  
 Protein Binding  
 Rats  
 \*Sulphydryl Compounds: PD, pharmacology  
 Thioglucosides: PD, pharmacology  
 Valine: AA, analogs & derivatives  
 Valine: PD, pharmacology

L22 ANSWER 13 OF 14 MEDLINE  
 AN 76220552 MEDLINE  
 TI The fate of phenylhydroxylamine in human red cells.  
 AU Kiese M; Taeger K  
 SO NAUNYN-SCHMIEDEBERGS ARCHIVES OF PHARMACOLOGY, (1976 Jan 14) 292 (1)  
 59-66.  
 Journal code: NTQ. ISSN: 0028-1298.  
 CY GERMANY, WEST: Germany, Federal Republic of  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 7610  
 AB Phenylhydroxylamine added to human red cells under aerobic conditions and in the presence of glucose was partly reduced to aniline. About half the hydroxylamine was recovered as amine after a 2-hr incubation. The aniline, after acetylation, was identified as acetanilide by melting point, Rf-value in TCL as well as UV, IR, and NMR spectroscopy. The fate of the remaining phenylhydroxylamine was followed by use of 14C-labeled phenylhydroxylamine. About 30% of the total radioactivity was bound to hemoglobin or other proteins and about 20% was found in highly polar low-molecular substances which were insoluble in organic solvents. The elucidation of the sites at which phenylhydroxylamine was bound to hemoglobin was complicated by the lability of the bonds. When purified human hemoglobin had reacted with radioactive phenylhydroxylamine, large proportions of the radioactivity bound to hemoglobin were removed by treatment with acid or with PMB for separation of alpha- and beta-chains. The radioactive compound liberated from hemoglobin by acid was found to be aniline. After reaction with phenylhydroxylamine the number of SH groups titrable with PMB was found to be diminished. Pretreatment of hemoglobin with N-ethylmaleimide or PMB decreased the amount of phenylhydroxylamine bound to hemoglobin but did not fully prevent the reaction. Tryptic digestion of hemoglobin after reaction with radioactive phenylhydroxylamine yielded tryptic peptides with lower specific activity than that of hemoglobin. Chymotryptic digestion of the tryptic core yielded a core with specific activity much higher than that of hemoglobin. Fingerprinting of the tryptic or chymotryptic hydrolyzates showed the presence of peptides with high and other ones with low or no radioactivity and of radioactive compounds which did not react with ninhydrin. In the covalent binding of phenylhydroxylamine to globin the SH group beta93 plays an important role, but other yet unknown sites are also reactive.  
 CT Check Tags: Human



Acetanilides: BL, blood  
 Aniline Compounds: BL, blood  
 Binding Sites  
 \*Erythrocytes: ME, metabolism  
 Glucose: PD, pharmacology  
**Hemoglobins: ME, metabolism**  
 \*Hydroxylamines: BL, blood  
 Lactates: PD, pharmacology  
**Methemoglobin: BI, biosynthesis**  
**Nitroso Compounds: BL, blood**  
**Sulphydryl Compounds: BL, blood**

L22 ANSWER 14 OF 14 MEDLINE  
 AN 74304967 MEDLINE  
 TI Nitrogen oxidation in ferrihaemoglobin formation.  
 AU Kiese M  
 SO XENOBIOTICA, (1971 Jul-Oct) 1 (4) 553-62. Ref: 62  
 Journal code: XQU. ISSN: 0049-8254.  
 CY ENGLAND: United Kingdom  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 LA English  
 FS Priority Journals  
 EM 7412  
 CT Check Tags: Animal; Comparative Study  
 \*Amines: BL, blood  
 Amines: PD, pharmacology  
 Blood Glucose  
 Dogs  
 Erythrocytes: DE, drug effects  
 Erythrocytes: EN, enzymology  
 \*Erythrocytes: ME, metabolism  
**Free Radicals**  
 Glucose: PD, pharmacology  
 \***Hemoglobins: BI, biosynthesis**  
**Hemoglobins: ME, metabolism**  
 Iron  
 Kinetics  
 Lactates: ME, metabolism  
 Lactates: PD, pharmacology  
**Nitroso Compounds: BL, blood**  
 NADP  
 Oxidation-Reduction  
 Oxidoreductases: BL, blood  
**Oxyhemoglobins: ME, metabolism**  
 Spectrophotometry, Ultraviolet  
 Structure-Activity Relationship  
 Time Factors

L23 ANSWER 1 OF 13 MEDLINE  
 AN 97050249 MEDLINE  
 TI Redox modulation of L-type calcium channels in ferret ventricular myocytes. Dual mechanism regulation by nitric oxide and S-nitrosothiols.  
 AU Campbell D L; Stamler J S; Strauss H C

CS Department of Pharmacology, Duke University Medical Center, Durham,  
North Carolina 27710, USA.

NC HL02582 (NHLBI)  
HL19216 (NHLBI)  
HL54314 (NHLBI)  
+

SO JOURNAL OF GENERAL PHYSIOLOGY, (1996 Oct) 108 (4) 277-93.  
Journal code: I8N. ISSN: 0022-1295.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9704

EW 19970403

AB The effects of NO-related activity and cellular thiol redox state on  
basal L-type calcium current, I<sub>Ca,L</sub>, in ferret right ventricular  
myocytes were studied using the patch clamp technique. SIN-1, which  
generates both NO. and O<sub>2</sub><sup>-</sup>, either inhibited or stimulated I<sub>Ca,L</sub>. In  
the presence of superoxide dismutase only inhibition was seen.  
8-Br-cGMP also inhibited I<sub>Ca,L</sub>, suggesting that the NO inhibition is  
cGMP-dependent. On the other hand, S-nitrosothiols (RSNOs), which  
donate NO<sup>+</sup>, stimulated I<sub>Ca,L</sub>. RSNO effects were not dependent upon  
cell permeability, modulation of SR Ca<sup>2+</sup> release, activation of  
kinases, inhibition of phosphatases, or alterations in cGMP levels.  
Similar activation of I<sub>Ca,L</sub> by thiol oxidants, and reversal by thiol  
reductants, identifies an allosteric thiol-containing "redox switch"  
on the L-type calcium channel subunit complex by which NO/O<sub>2</sub><sup>-</sup> and  
NO<sup>+</sup> transfer can exert effects opposite to those produced by NO. In  
sum, our results suggest that: (a) both indirect (cGMP-dependent)  
and direct (S-nitrosylation/oxidation) regulation of ventricular  
I<sub>Ca,L</sub>, and (b) sarcolemma thiol redox state may be an important  
determinant of I<sub>Ca,L</sub> activity.

L23 ANSWER 2 OF 13 MEDLINE

AN 96390846 MEDLINE

TI Nitrosative stress: activation of the transcription factor OxyR.

AU Hausladen A; Privalle C T; Keng T; DeAngelo J; **Stamler J S**

CS Department of Medicine, Duke University Medical Center Durham, North  
Carolina 27710, USA.

NC HL02582 (NHLBI)  
HL52529 (NHLBI)

SO CELL, (1996 Sep 6) 86 (5) 719-29.  
Journal code: CQ4. ISSN: 0092-8674.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9612

AB Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) imposes an oxidative stress to Escherichia  
coli that is manifested by oxidation of glutathione and related  
redox-sensitive targets. OxyR is a thiol-containing transcriptional  
activator whose oxidation controls the expression of genes involved  
in H<sub>2</sub>O<sub>2</sub> detoxification. Here we report that certain S-nitrosothiols  
(RSNOs) impose what we term a "nitrosative stress" to E. coli,  
evidenced by lowering of intracellular thiol and the transcriptional  
activation of OxyR by S-nitrosylation. This cellular and genetic  
response determines the metabolic fate of RSNOs and thereby

contributes to bacterial rescue from stasis. Our studies reveal that signaling by S-nitrosylation can extend to the level of transcription and describe a metabolic pathway that constitutes an adaptation to nitrosative stress.

L23 ANSWER 3 OF 13 MEDLINE  
 AN 96209801 MEDLINE  
 TI Polynitrosylated proteins: characterization, bioactivity, and functional consequences.  
 AU Simon D I; Mullins M E; Jia L; Gaston B; Singel D J; **Stamler J S**  
 CS Department of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA 02115, USA.  
 NC HL02582 (NHLBI)  
 HL02768 (NHLBI)  
 HL52529 (NHLBI)  
 SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 May 14) 93 (10) 4736-41.  
 Journal code: PV3. ISSN: 0027-8424.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Cancer Journals; Priority Journals  
 EM 9609  
 AB Chemical modification of proteins is a common theme in their regulation. Nitrosylation of protein sulfhydryl groups has been shown to confer nitric oxide (NO)-like biological activities and to regulate protein functions. Several other nucleophilic side chains -- including those with hydroxyls, amines, and aromatic carbons -- are also potentially susceptible to nitrosative attack. Therefore, we examined the reactivity and functional consequences of nitros(yl)ation at a variety of nucleophilic centers in biological molecules. Chemical analysis and spectroscopic studies show that nitrosation reactions are sustained at sulfur, oxygen, nitrogen, and aromatic carbon centers, with thiols being the most reactive functionality. The exemplary protein, BSA, in the presence of a 1-, 20-, 100-, or 200-fold excess of nitrosating equivalents removes 0.6 +/- 0.2, 3.2 +/- 0.4, 18 +/- 4, and 38 +/- 10, respectively, moles of NO equivalents per mole of BSA from the reaction medium; spectroscopic evidence shows the proportionate formation of a polynitrosylated protein. Analogous reaction of tissue-type plasminogen activator yields comparable NO protein stoichiometries. Disruption of protein tertiary structure by reduction results in the preferential nitrosylation of up to 20 thus-exposed thiol groups. The polynitrosylated proteins exhibit antiplatelet and vasodilator activity that increases with the degree of nitrosation, but S-nitroso derivatives show the greatest NO-related bioactivity. Studies on enzymatic activity of tissue-type plasminogen activator show that polynitrosylation may lead to attenuated function. Moreover, the reactivity of tyrosine residues in proteins raises the possibility that NO could disrupt processes regulated by phosphorylation. Polynitrosylated proteins were found in reaction mixtures containing interferon-gamma/lipopolysaccharide-stimulated macrophages and in tracheal secretions of subjects treated with NO gas, thus suggesting their physiological relevance. In conclusion, multiple sites on proteins are susceptible to attack by nitrogen oxides. Thiol groups are preferentially modified, supporting the

notion that S-nitrosylation can serve to regulate protein function. Nitrosation reactions sustained at additional nucleophilic centers may have (patho)physiological significance and suggest a facile route by which abundant NO bioactivity can be delivered to a biological system, with specificity dictated by protein substrate.

L23 ANSWER 4 OF 13 MEDLINE

AN 95361522 MEDLINE

TI S-nitrosothiols and the bioregulatory actions of nitrogen oxides through reactions with thiol groups.

AU **Stamler J S**

CS Division of Respiratory Medicine, Duke University Medical Center, Durham, NC 27710, USA..

NC HL 02582-011 (NHLBI)

SO CURRENT TOPICS IN MICROBIOLOGY AND IMMUNOLOGY, (1995) 196 19-36.

Ref: 92

Journal code: DWQ. ISSN: 0070-217X.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LA English

EM 9511

AB The reactivity of selected RS-NOs has led to the misconception that these compounds are uniformly unstable under physiological conditions. Moreover, current evidence supports the notion that biological responses elicited by RS-NOs may result from either liberation of nitric oxide or from NO group transfer chemistry involving either NO<sup>+</sup> or NO<sup>-</sup>. Some evidence suggests that such reactions may be enzymatically controlled. The data supporting the potential biological relevance of RS-NOs include: (1) evidence that these compounds form under physiological conditions; (2) their identification in insects, lower mammals, and several human biological systems; and (3) findings that RS-NOs possess a wide range of biological activities, including antimicrobial effects, vasodilation, platelet inhibition, bronchodilation and inhibition of intestinal motility, while being relatively resistant to reactions with O<sub>2</sub> and O<sub>2</sub><sup>-</sup> associated with NO toxicity. It is further noteworthy that biological activity of RS-NO is often not related to the propensity to liberate NO, and these adducts are generally more potent and selective in their action than NO itself (Stamler et al. 1989; Cooke et al. 1990; Rockett et al. 1991; Jansen et al. 1991; Lipton et al. 1993). The data presented here support the idea that RS-NO may be involved in stabilizing nitric oxide-like bioactivity, in transporting and targeting the NO group to specific (thioregulatory) effector sites, in mitigating the cytotoxic effects of nitric oxide that result from reaction with oxygen species, and may serve to regulate protein function in a posttranslational modification akin, perhaps, to phosphorylation. The recently demonstrated NO group transfer reactions to plasma membrane proteins containing reactive sulfhydryls (Lipton et al. 1993; Stamler 1994) also raises the possibility of signal transduction initiated through more traditional "agonist-receptor" mediated pathways.

L23 ANSWER 5 OF 13 MEDLINE

AN 95251375 MEDLINE

TI NO<sup>+</sup>, NO, and NO<sup>-</sup> donation by S-nitrosothiols: implications for

regulation of physiological functions by S-nitrosylation and acceleration of disulfide formation.

AU Arnelle D R; **Stamler J S**  
 CS Duke University Medical Center, Department of Respiratory Medicine, Durham, North Carolina 27710, USA.  
 NC HLO02582 (NHLBI)  
 HL52529 01  
 SO ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS, (1995 Apr 20) 318 (2) 279-85.  
 Journal code: 6SK. ISSN: 0003-9861.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals; Cancer Journals  
 EM 9508  
 AB The biological effects of S-nitrosothiols have been attributed to homolytic cleavage of the S-N bond with release of nitric oxide (NO.). Rates of NO. release from several S-nitrosothiols were determined by monitoring the oxidation of oxymyoglobin to metmyoglobin at pH 7.4; half-lives for oxymyoglobin oxidation ranged from seconds to hours. Transnitrosation reactions between S-nitrosothiols and thiol-containing amino acids, peptides, and proteins, which indicate the ability of nitrosothiols to act as nitrosyl (NO+) donors, occurred more rapidly than spontaneous NO. release. Decomposition of S-nitrosodithiols were examined as models for the reaction of nitrogen oxides with vicinal thiols on proteins. Rapid disulfide formation was accompanied by formation of hydroxylamine and nitrous oxide, indicative of nitroxyl (NO-) release. Taken together, these model studies demonstrate the ability of S-nitrosothiols to act as NO+, NO., and NO- donors under physiological conditions. Transnitrosation and acceleration of disulfide formation suggest mechanisms of regulation of protein function through the intermediacy of nitrosothiols, and support the notion that biological activities of S-nitrosothiols may be associated with heterolytic as well as homolytic mechanisms of decomposition.

L23 ANSWER 6 OF 13 MEDLINE

AN ~~95015008~~ MEDLINE

TI In vivo transfer of nitric oxide between a plasma protein-bound reservoir and low molecular weight thiols.  
 AU Scharfstein J S; Keaney J F Jr; Slivka A; Welch G N; Vita J A; **Stamler J S**; Loscalzo J  
 CS Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts..  
 NC HL40411 (NHLBI)  
 HL48743 (NHLBI)  
 HL53919 (NHLBI)  
 +  
 SO JOURNAL OF CLINICAL INVESTIGATION, (1994 Oct) 94 (4) 1432-9.  
 Journal code: HS7. ISSN: 0021-9738.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
 EM 9501  
 AB Plasma albumin reacts with nitric oxide (NO) to form the bioactive

adduct, S-nitroso-albumin (S-NO-albumin). The limited intracellular access of S-NO-albumin suggests the need for a vascular transfer mechanism of NO from a large plasma S-NO-albumin pool to effect biologic function. To study the role of low molecular weight (LMW) thiols in NO transfer in vivo, we administered intravenous S-NO-albumin (1-300 nmol/kg) to rabbits before and after an intravenous infusion of L-cysteine or N-acetyl-L-cysteine. S-NO-albumin produced dose-dependent hypotension that was significantly augmented by prior infusion of either LMW thiol. LMW thiol infusion significantly accelerated the rate of onset and reduced the duration of action of the hypotension induced by S-NO-albumin. The hemodynamic effects of S-NO-albumin after pretreatment with LMW thiols were mimicked by administration of the corresponding LMW S-nitrosothiol. The transfer of NO from albumin to L-cysteine was directly measured in rabbit plasma using a novel technique that couples high performance liquid chromatography to electrochemical detection. These data demonstrate that NO exchange between plasma protein thiol-bound NO and available LMW thiol pools (transnitrosation) occurs in vivo.

L23 ANSWER 7 OF 13 MEDLINE  
 AN 94157807 MEDLINE  
 TI Relaxation of human bronchial smooth muscle by S-nitrosothiols in vitro.  
 AU Gaston B; Drazen J M; Jansen A; Sugarbaker D A; Loscalzo J; Richards W; **Stamler J S**  
 CS Ina Sue Perimutter Laboratory, Children's Hospital, Boston, Massachusetts..  
 NC HL19170 (NHLBI)  
 HL40411 (NHLBI)  
 HL48743 (NHLBI)  
 +  
 SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994 Feb) 268 (2) 978-84.  
 Journal code: JP3. ISSN: 0022-3565.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 LA English  
 FS Priority Journals  
 EM 9406  
 AB S-Nitrosothiols (RS-NO) relax tracheal smooth muscle from a variety of animal species, and may have physiological relevance. We therefore studied their effects on human bronchial smooth muscle. S-Nitroso adducts of glutathione, cysteine, N-acetylcysteine and bovine serum albumin relaxed tissues contracted with methacholine with mean IC50 +/- S.E.M. of 3.3 (+/- 14), 22 (+/- 45), 25 (+/- 22) and 36 (+/- 7.1) microM, respectively; they were more potent as inhibitory agonists than the corresponding reduced thiol, NaNO2, or theophylline, but less potent than isoproterenol (P < .001). Despite large differences in their molecular weights and dissociation kinetics, the IC50 of these RS-NO did not differ significantly from one another, from nitric oxide (NO.) or from sodium nitroprusside. Consistent with the role of cyclic GMP (cGMP) in mediating relaxation responses, S-nitroso-N-acetyl cysteine (S-NO-AC) (100 microM) increased tissue cGMP levels 4-fold, and 8-bromo-cGMP caused modest tissue relaxation which was potentiated by the phosphodiesterase inhibitor, dipyridamole (1 microM). However, the

guanylyl cyclase inhibitors, methylene blue (100 microM) and LY 83583 (50 microM), failed to modify the relaxation response to S-NO-AC (sodium nitroprusside and NO.), while altering the accumulation of cGMP. Further, hemoglobin (100 microM) failed to inhibit relaxation by S-NO-AC. (ABSTRACT TRUNCATED AT 250 WORDS)

L23 ANSWER 8 OF 13 MEDLINE

AN 93271106 MEDLINE

TI Antiplatelet properties of protein S-nitrosothiols derived from nitric oxide and endothelium-derived relaxing factor.

AU Simon D I; **Stamler J S**; Jaraki O; Keaney J F; Osborne J A; Francis S A; Singel D J; Loscalzo J

CS Department of Medicine, Harvard University, Boston..

NC HL-40411 (NHLBI)

HL-43344 (NHLBI)

HL-48734 (NHLBI)

+

SO ARTERIOSCLEROSIS AND THROMBOSIS, (1993 Jun) 13 (6) 791-9.

Journal code: AZ1. ISSN: 1049-8834.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9309

AB S-nitrosothiols may serve as carriers in the mechanism of action of endothelium-derived relaxing factor (EDRF) by stabilizing the labile nitric oxide (NO) radical from inactivation by reactive species in the physiological milieu and by delivering NO to the heme activator site of guanylyl cyclase. Low-molecular-weight thiols, such as cysteine and glutathione, form S-nitrosothiol adducts with vasodilatory and antiplatelet properties, and protein thiols can interact in the presence of NO and/or EDRF to form uniquely stable S-nitroso-proteins. We now show that the S-nitroso-proteins, S-nitroso-albumin, S-nitroso-tissue type plasminogen activator, and S-nitroso-cathepsin B, have potent antiplatelet effects with an IC50 of approximately 1.5 microM. In the dog, S-nitroso-albumin inhibits ex vivo platelet aggregation and significantly prolongs the template bleeding time from 2.15 +/- 0.13 (mean +/- SEM) to 9.70 +/- 1.24 minutes. The antiplatelet action of S-nitroso-proteins is associated with the stimulation of guanylyl cyclase and a significant decrease in fibrinogen binding to platelets. S-Nitroso-proteins undergo thiol-nitrosothiol exchange with low-molecular-weight thiols to form low-molecular-weight S-nitroso-thiols, and they also interact directly with the platelet surface, both of which processes facilitate generation of NO. These data suggest that S-nitroso-proteins are potent antiplatelet agents and may be intermediates in the antiplatelet mechanism of EDRF action.

L23 ANSWER 9 OF 13 MEDLINE

AN 92390394 MEDLINE

TI S-nitrosylation of tissue-type plasminogen activator confers vasodilatory and antiplatelet properties on the enzyme.

AU **Stamler J S**; Simon D I; Jaraki O; Osborne J A; Francis S; Mullins M; Singel D; Loscalzo J

CS Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.

NC HL40411 (NHLBI)

HL43344 (NHLBI)  
RRO4870

+

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES  
OF AMERICA, (1992 Sep 1) 89 (17) 8087-91.  
Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9212

AB Tissue-type plasminogen activator (t-PA) reacts upon exposure to endothelium-derived relaxing factor (EDRF) by way of the enzyme's single free sulfhydryl (Cys-83) to form a stable S-nitrosothiol protein adduct. S-nitrosylation endows t-PA with potent vasodilatory and antiplatelet properties that are accompanied by elevations in intracellular cyclic GMP analogous to those induced by low molecular weight (e.g., S-nitroso amino acid) S-nitrosothiols. Moreover, this chemical modification does not adversely affect the catalytic efficiency of t-PA, the fibrin stimulation of this activity, the binding of t-PA to fibrinogen, or the interaction of the enzyme with its physiologic serine protease inhibitor, plasminogen-activator inhibitor type I. The coupling of vasodilatory, antiplatelet, and fibrinolytic properties in one molecule makes the S-nitrosylated t-PA a unique molecular species and may provide insight into the mechanisms by which the endothelium maintains vessel patency. These data also suggest a pharmacologic approach to treatment of thromboocclusive disorders.

L23 ANSWER 10 OF 13 MEDLINE

AN 92366524 MEDLINE

TI Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin.

AU **Stamler J S**; Jaraki O; Osborne J; Simon D I; Keaney J; Vita J; Singel D; Valeri C R; Loscalzo J

CS Department of Medicine, Harvard University, Cambridge, MA 02138.

NC HL40411 (NHLBI)

HL43344 (NHLBI)

K08HL02582 (NHLBI)

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES  
OF AMERICA, (1992 Aug 15) 89 (16) 7674-7.

Journal code: PV3. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals; Cancer Journals

EM 9211

AB We have recently shown that nitric oxide or authentic endothelium-derived relaxing factor generated in a biologic system reacts in the presence of specific protein thiols to form S-nitrosoprotein derivatives that have endothelium-derived relaxing factor-like properties. The single free cysteine of serum albumin, Cys-34, is particularly reactive toward nitrogen oxides (most likely nitrosonium ion) under physiologic conditions, primarily because of its anomalously low pK; given its abundance in plasma, where it accounts for approximately 0.5 mM thiol, we hypothesized that this plasma protein serves as a reservoir for nitric oxide produced by



the endothelial cell. To test this hypothesis, we developed a methodology, which involves UV photolytic cleavage of the S--NO bond before reaction with ozone for chemiluminescence detection, with which to measure free nitric oxide, S-nitrosothiols, and S-nitrosoproteins in biologic systems. We found that human plasma contains approximately 7 microM S-nitrosothiols, of which 96% are S-nitrosoproteins, 82% of which is accounted for by S-nitroso-serum albumin. By contrast, plasma levels of free nitric oxide are only in the 3-nM range. In rabbits, plasma S-nitrosothiols are present at approximately 1 microM; 60 min after administration of NG-monomethyl-L-arginine at 50 mg/ml, a selective and potent inhibitor of nitric oxide synthetases, S-nitrosothiols decreased by approximately 40% (greater than 95% of which were accounted for by S-nitrosoproteins, and approximately 80% of which was S-nitroso-serum albumin); this decrease was accompanied by a concomitant increase in mean arterial blood pressure of 22%. These data suggest that naturally produced nitric oxide circulates in plasma primarily complexed in S-nitrosothiol species, principal among which is S-nitroso-serum albumin. This abundant, relatively long-lived adduct likely serves as a reservoir with which plasma levels of highly reactive, short-lived free nitric oxide can be regulated for the maintenance of vascular tone.

L23 ANSWER 11 OF 13 MEDLINE

AN 92219124 MEDLINE

TI The relaxant properties in guinea pig airways of S-nitrosothiols.

AU Jansen A; Drazen J; Osborne J A; Brown R; Loscalzo J; **Stamler J**

**S**

CS Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts..

NC HL19170 (NHLBI)

HL40411 (NHLBI)

HL43344 (NHLBI)

+

SO JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1992 Apr) 261 (1) 154-60.

Journal code: JP3. ISSN: 0022-3565.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9207

AB Several cellular constituents of the lung have the capacity to synthesize a factor capable of relaxing smooth muscle which has the physicochemical properties of nitric oxide (NO). In other systems, it has been shown that NO may be stabilized in the plasma and cellular milieu by reduced thiol in the form of an S-nitrosothiol (RS-NO). These compounds have half-lives that are significantly greater than that of NO, and also retain the vasorelaxant activity of NO, which is mediated by activating guanylate cyclase and raising cyclic GMP levels. The effects of RS-NO and their potential mechanism of action on airways, however, have not been previously investigated. In this study, we have examined the smooth muscle relaxant properties of several biological and synthetic RS-NO on guinea pig trachea. Our data reveal that RS-NO are generally potent airway smooth muscle relaxants with at least a partial effect through stimulation of cyclic GMP. Relaxations were attenuated

significantly by the guanylate cyclase inhibitor methylene blue (P less than .05), and RS-NO-induced increases in cyclic GMP were demonstrated (P less than .0005). The IC50 values for S-nitroso-glutathione, S-nitroso-cysteine, S-nitroso-homocysteine, S-nitroso-N-acetylcysteine, S-nitroso-penicillamine and S-nitroso-captopril were 0.99 +/- 0.09, 3.2 +/- 0.2, 2.1 +/- 0.3, 2.1 +/- 0.8, 1.8 +/- 0.8 and 20 +/- 0.7 microM (mean +/- S.E.M.), respectively. In this system isoproterenol has an IC50 of 0.016 microM and theophylline an IC50 of 74 microM, making the relaxant properties of these NO derivatives of potential pharmacological and physiological relevance.

L23 ANSWER 12 OF 13 MEDLINE  
 AN 92043166 MEDLINE  
 TI The antiplatelet effects of organic nitrates and related nitroso compounds in vitro and in vivo and their relevance to cardiovascular disorders [see comments].  
 CM Comment in: J Am Coll Cardiol 1991 Nov 15;18(6):1537-8  
 AU **Stamler J S**; Loscalzo J  
 CS Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts 02115..  
 NC HL 40411 (NHLBI)  
 HL 43344 (NHLBI)  
 HL 01877 (NHLBI)  
 +  
 SO JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, (1991 Nov 15) 18 (6) 1529-36. Ref: 104  
 Journal code: H50. ISSN: 0735-1097.  
 CY United States  
 DT Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LA English  
 FS Abridged Index Medicus Journals; Priority Journals  
 EM 9202  
 AB Organic nitrates, cornerstones of antianginal therapy, are believed to exert their principal anti-ischemic benefit by relaxing vascular smooth muscle. Recent evidence suggests that these compounds and related nitro(so) vasodilators are also potent platelet inhibitors. In view of the well recognized role of thrombotic events mediated by platelets in acute coronary syndromes, the antiplatelet effect of nitrates may also be of mechanistic importance in the treatment of these disorders. This review details the biochemical mechanism by which nitro(so) compounds inhibit platelet function and summarizes the in vitro and in vivo evidence that supports their antithrombotic effects.

L23 ANSWER 13 OF 13 MEDLINE  
 AN 90372437 MEDLINE  
 TI Flow stimulates endothelial cells to release a nitrovasodilator that is potentiated by reduced thiol.  
 AU Cooke J P; **Stamler J**; Andon N; Davies P F; McKinley G;  
 Loscalzo J  
 CS Division of Vascular Medicine and Atherosclerosis, Brigham and Women's Hospital, Boston 02115..  
 NC HL-40411 (NHLBI)  
 HL-36028 (NHLBI)

HL-36049 (NHLBI)

+

SO AMERICAN JOURNAL OF PHYSIOLOGY, (1990 Sep) 259 (3 Pt 2) H804-12.  
Journal code: 3U8. ISSN: 0002-9513.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 9012

AB We designed a novel system to study flow-mediated endothelium-dependent vasodilation. Vascular rings of rabbit thoracic aorta were mounted for isometric tension recording in a flow chamber filled with physiological saline solution. The flow chamber contained a stir bar and was mounted on a magnetic stirrer to induce vortical flow. Norepinephrine (NE,  $10^{-6}$  M) induced contraction of the vascular rings. Bovine endothelial cells on microcarrier beads added to the chamber had little effect on contraction to NE in the absence of flow. Flow induced endothelium-dependent relaxation of the vascular rings that was dependent on the flow rate. Relaxations were annulled or reversed to a contraction with methylene blue, bovine hemoglobin, or N-monomethyl-L-arginine. Conversely, N-acetyl-L-cysteine augmented the flow-mediated relaxation. Furthermore, in the presence of N-acetyl-L-cysteine, the half-life of the endothelium-dependent relaxing factor was increased. In conclusion, the stimulus of flow induces the release by endothelial cells of a diffusible, short-lived factor with the attributes of a nitrovasodilator. The action of this endogenous vasodilator is augmented by the reduced thiol N-acetyl-L-cysteine.

=> d his

(FILE 'HOME' ENTERED AT 13:53:52 ON 24 JUN 1997)

FILE 'HCAPLUS' ENTERED AT 13:54:30 ON 24 JUN 1997

ACT CELSA616/A

L1 158 SEA FILE=HCAPLUS ABB=ON "STAMLER J"/AU OR "STAMLER J S"/

ACT CELSA/A

L2 ( 11)SEA FILE=HCAPLUS ABB=ON NITROSOHB/OBI OR NITROSOHEMOGLOB  
L3 ( 209)SEA FILE=HCAPLUS ABB=ON (NITROSO/OBI OR NITROSYL/OBI) (L  
L4 ( 119)SEA FILE=HCAPLUS ABB=ON NITROSYLHEMOGLOBIN/OBI OR NITROS  
L5 249 SEA FILE=HCAPLUS ABB=ON L4 OR L3 OR L2

L6 4 S L1 AND L5

=> d .ca 1-4

L6 ~~ANSWER 1 OF 4 HCAPLUS~~ COPYRIGHT 1997 ACS

AN 1997:310017 HCAPLUS

DN 126:274520

TI Method for measuring **nitrosyl** [Fe(II)]-hemoglobin  
in health and disease

IN **Stamler, Jonathan S.**

PA Duke University Medical Center, USA; Stamler, Jonathan S.

SO PCT Int. Appl., 18 pp.

CODEN: PIXXD2

PI WO 9710493 A1 970320

DS TT, W UA, W UG, W US, W UZ, W VN, W AM, W AZ, W BY, W KG, W KZ, W  
MD, W RU, W TJ, W TM, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ,  
LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL,  
PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ,  
VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM  
RW: AT, BE, BF, BJ, CF, CG, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT,  
LU, MC, NL, PT, SE

AI WO 96-US14660 960913

PRAI US 95-3801 950915

US 96-616259 960315

DT Patent

LA English

AB Nitrosyl [Fe(II)]-Hb can be detected in biol. samples, e.g., blood,  
by using a method that involves injection of samples into a  
photolysis cell, prior to detection of chemiluminescence generated  
by the reaction between nitric oxide and ozone. This method is  
useful for monitoring the levels of nitric oxide bioactivity in both  
normal physiol. states and disease states, such as septic shock,  
atherosclerosis, thrombosis, hyperhomocysteinemia, pulmonary  
hypertension, malignancy, infections, and central nervous system  
disorders.

IC ICM G01N021-63

ICS G01N021-76; G01N033-68

CC 9-5 (Biochemical Methods)

Section cross-reference(s): 3, 13, 14

ST blood **nitrosylHb** detn photolysis chemiluminescence  
disease; nitroso thiol detn photolysis chemiluminescence

- IT Serum albumin  
RL: ANT (Analyte); ANST (Analytical study)  
(S-nitroso; nitrosyl [Fe(II)]-Hb  
detn. by photolysis/chemiluminescence in relation to nitric oxide  
metab.)
- IT Hemoglobins  
Thiols (organic), analysis  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);  
BIOL (Biological study); USES (Uses)  
(S-nitroso; nitrosyl [Fe(II)]-Hb  
detn. by photolysis/chemiluminescence in relation to nitric oxide  
metab.)
- IT Emission spectrometers  
(chemiluminescence; nitrosyl [Fe(II)]-Hb  
detn. by photolysis/chemiluminescence in relation to nitric oxide  
metab.)
- IT Atherosclerosis  
Blood analysis  
Central nervous system diseases  
Diseases (animal)  
Erythrocyte  
Infection  
Photolysis  
Pulmonary hypertension  
Septic shock  
Thrombosis  
Tumors (animal)  
(nitrosyl [Fe(II)]-Hb detn. by  
photolysis/chemiluminescence in relation to nitric oxide metab.)
- IT Hemoglobins  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);  
BIOL (Biological study); USES (Uses)  
(nitrosylHbs; nitrosyl [Fe(II)]-Hb detn. by  
photolysis/chemiluminescence in relation to nitric oxide metab.)
- IT Proteins (specific proteins and subclasses)  
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study);  
BIOL (Biological study); USES (Uses)  
(sulfoproteins, S-nitroso; nitrosyl [Fe(II)]-  
Hb detn. by photolysis/chemiluminescence in relation to  
nitric oxide metab.)
- IT 6027-13-0, Homocysteine  
RL: ARG (Analytical reagent use); RCT (Reactant); ANST (Analytical  
study); USES (Uses)  
(metabolic disorders, hyperhomocysteinemia; nitrosyl  
[Fe(II)]-Hb detn. by photolysis/chemiluminescence in  
relation to nitric oxide metab.)
- IT 51209-75-7, S-Nitroso-L-cysteine 56577-02-7, S-  
Nitroso-N-acetyl-L-cysteine 57564-91-7,  
S-Nitrosoglutathione  
RL: ANT (Analyte); ANST (Analytical study)  
(nitrosyl [Fe(II)]-Hb detn. by  
photolysis/chemiluminescence in relation to nitric oxide metab.)
- IT 10102-43-9, Nitric oxide, analysis  
RL: ANT (Analyte); BPR (Biological process); MFM (Metabolic  
formation); RCT (Reactant); ANST (Analytical study); BIOL  
(Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(nitrosyl [Fe(II)]-Hb detn. by

photolysis/chemiluminescence in relation to nitric oxide metab.)  
 IT 10028-15-6, Ozone, reactions  
 RL: ARG (Analytical reagent use); RCT (Reactant); ANST (Analytical study); USES (Uses)  
 (nitrosyl [Fe(II)]-Hb detn. by  
 photolysis/chemiluminescence in relation to nitric oxide metab.)

~~L6 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 1997 ACS~~  
 AN 1996:761663 HCAPLUS  
 DN 126:37023  
 TI Nitrosylated heme proteins as blood substitutes  
 IN **Stamler, Jonathan**  
 PA Brigham and Women's Hospital, USA  
 SO PCT Int. Appl., 130 pp.  
 CODEN: PIXXD2  
 PI WO 9630006 A1 961003  
 DS W: AU, CA, JP  
 RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE  
 AI WO 96-US3866 960325  
 PRAI US 95-409720 950324  
 DT Patent  
 LA English  
 AB Blood substitutes comprises a heme protein to which NO or NO2 group is linked directly or indirectly. Tissue plasminogen activator (t-PA) was S-nitrosylated (prepn. given) and thrombolytic, anti-platelet, and vasodilator effects of S-NO-t-PA were studied.  
 IC ICM A61K031-14  
 ICS A61K031-715; A61K031-765; A61K038-16; C07D307-82  
 CC 63-3 (Pharmaceuticals)  
 Section cross-reference(s): 34  
 IT **Hemoglobins**  
 RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (nitrosyl-; compns. contg. nitrosylated heme proteins as blood substitutes)

~~L6 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 1997 ACS~~  
 AN 1996:324257 HCAPLUS  
 DN 125:54485  
 TI **S-Nitrosohemoglobin**: A new activity of blood involved in regulation of blood pressure  
 AU Jia, Lee; Bonaventura, Celia; Bonaventura, Joseph; **Stamler, Jonathan S.**  
 CS Medical Center, Duke University, Durham, NC, 27710, USA  
 SO Portland Press Proc. (1996), 10(Biology of Nitric Oxide Part 5), 14  
 CODEN: POPPEF  
 DT Journal  
 LA English  
 AB New allosteric and/or electronic properties of Hb involved in regulation of vasomotor tone argue against the importance of free NO in transduction of such NO related activity, and suggest that S-NitrosoHbs could be used to overcome the hypertensive side effects of Hb-based blood substitutes.  
 CC 13-6 (Mammalian Biochemistry)  
 ST **nitrosoHb** NO blood pressure

IT Blood pressure  
(S-NitrosoHb in regulation of blood pressure)

IT **Hemoglobins**  
RL: BAC (Biological activity or effector, except adverse); THU  
(Therapeutic use); BIOL (Biological study); USES (Uses)  
(nitrosyl-, S-NitrosoHb in regulation of  
blood pressure)

IT 10102-43-9, Nitric oxide, biological studies  
RL: BAC (Biological activity or effector, except adverse); BIOL  
(Biological study)  
(S-NitrosoHb in regulation of blood pressure)

L6 ANSWER-4-OF-4--HCAPLUS COPYRIGHT 1997 ACS  
AN 1996:182211 HCAPLUS  
DN 124:298544

TI **S-Nitrosohemoglobin**: a dynamic activity of blood involved  
in vascular control

AU Jia, Li; Bonaventura, Celia; Bonaventura, Joseph; **Stamler,**  
**Jonathan S.**  
CS Dep. Med., Duke Univ. Med. Cent., Durham, NC, 27710, USA  
SO Nature (London) (1996), 380(6571), 221-6  
CODEN: NATUAS; ISSN: 0028-0836

DT Journal  
LA English

AB A dynamic cycle exists in which Hb is S-nitrosylated in the lung  
when red blood cells are oxygenated, and the NO group is released  
during arterial-venous transit. The vasoactivity of S-nitrosoHb is  
promoted by the erythrocytic export of S-nitrosothiols. These  
findings highlight newly discovered allosteric and electronic  
properties of Hb that appear to be involved in the control of blood  
pressure and which may facilitate efficient delivery of oxygen of  
tissues. The role of S-nitrosoHb in the transduction of NO-related  
activities may have therapeutic applications.

CC 63-3 (Pharmaceuticals)  
Section cross-reference(s): 13

ST **nitrosoHb** nitrosothiol NO blood vascular control

IT Animal respiration  
Blood substitutes and Plasma expanders  
Blood vessel  
Erythrocyte  
Lung  
Signal transduction, biological  
(S-nitrosoHb in dynamic activity of blood involved in  
vascular control)

IT Thiols, biological studies  
RL: BPR (Biological process); MFM (Metabolic formation); BIOL  
(Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(S-nitroso, S-nitrosoHb in dynamic activity of blood  
involved in vascular control)

IT **Hemoglobins**  
RL: BPR (Biological process); MFM (Metabolic formation); BIOL  
(Biological study); FORM (Formation, nonpreparative); PROC (Process)  
(nitrosyl-, S-nitrosoHb in dynamic activity  
of blood involved in vascular control)

IT 10102-43-9, Nitrogen oxide (NO), biological studies  
RL: BPR (Biological process); BIOL (Biological study); PROC  
(Process)

Celsa 08/616,371

(S-nitrosoHb in dynamic activity of blood involved in  
vascular control)